Numerical and Experimental Analyses of Aerosol Deposition in a Novel and Standardized Human Nasal Cavity

by

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in Mechanical Engineering

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Abstract

This thesis presents an investigation of flow and aerosol deposition patterns in a model human nasal cavity using both experimental measurements and numerical simulations. A novel, standardized human nasal cavity model was created as part of this work by processing 30 sets of computed tomography (CT) scans of nasal airways of healthy subjects. Aerosol deposition in the novel, “Carleton-Civic” standardized geometry of the human nasal cavity was studied both numerically and experimentally. Inhalation flow rates varied from 30 to 90 L/min in the experiments, and aerosol droplets had diameters ranging from 1.71 to 9.14 μm , giving impaction parameters ranging from 123.3 to 2527.6 $\mu\text{m L/min}$. For the numerical simulations, both the RANS/EIM (Reynolds Averaged Navier-Stokes equations for the gas phase and Eddy-Interaction random walk Models for the particulate phase) and Large Eddy Simulations were used to better understand the limits of applicability and accuracy of standard numerical methods as available in many commercial packages.

Both experimental and simulated results showed that the mechanisms of aerosol deposition in the standardized nasal cavity were dominated by inertial impaction. Measured deposition data from the standardized nasal cavity transected cited *in vitro* data based on individual subjects. The data correlated very well with cited *in vivo* measurements but generally showed less aerosol deposition for a given value of the impaction parameter. Regional particle deposition characteristics within the nasal passages were also investigated both experimentally and numerically, and new trends of

regional deposition versus impaction parameter are discussed. These provide new insight into the general deposition behaviour of various sized aerosols within the human nasal cavity.

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Nomenclature

A	Cross-sectional area in the nasal airway [m^2]
A_{min}	Minimal cross-sectional area in the nasal airway [m^2]
a'	Constant in fitting equation of total particle deposition fraction
Ab	Absorption fraction of a sample measured by the spectrophotometer [-]
B	Bias limits or body force [N]
C_D	Drag coefficient [-]
C	Volumetric concentration of Vitamin E in the vitamin E solution [g/cm^3]
C_a	Added mass coefficient [-]
C_μ	A constant in the eddy diffusivity formula [-]
DF	Deposition fraction [-]
D	Diffusion coefficient [-]
d or d_p	Particle diameter [μm]
d_a	Aerodynamic diameter of a particle $(\rho_p/\rho_w)^{1/2}d_p$ [μm]
$\frac{D}{dt}$	Total time derivative for a fluid particle [-]
$\frac{d}{dt}$	Total time derivative for an aerosol particle (or for a fluid particle) [-]
$\overline{F}_{Drag}$	Drag force on aerosol particle due to the air [N]
$\overline{F}_{Saffmann}^\perp$	Saffman lift force [N]
f	Frequency of the aerosol generator (also used as an arbitrary function)
F	A function in the turbulence model (or in Appendix A, inertial body force [N])
g	Gravitational acceleration constant [m/s^2]
I	Volumetric concentration of non-volatile impurities [g/cm^3]; also used to denote turbulence intensity[-]
l_e or L_e	Length scale of the energy containing eddies [m]
l_t	Specified length scale at inlet [m]

In	Incident light on a sample in the spectrophotometer [-]
k	Boltzmann's constant (or turbulence kinetic energy) [-]
m	mass [kg]
$\dot{m}$	Mass flow rate of air [kg/s]
M	Number of particles or number of readings in measurement [-]
M_n	Masses of particles deposited in the nasal model [kg]
M_f	Masses of particles deposited in the filter [kg]
N	Vol times Ab[-]; also used to denote a random number[-]
P	Air pressure [Pa]
P_{gauge}	Gauge pressure of air [Pa]
P_r	Precision limit of the measured results [-]
Q	Volume flow rate of air [m ³ /s]
Q_S	Volume flow rate of vitamin E solution [m ³ /s]
Q_{SLPM}	Flow rate of air assuming atmospheric air density [m ³ /s]
r	Readings in experiment [-]
$\bar{r}$	Averaged result [-]
Re	Flow Reynolds number based on the pipe diameter and the area-average velocity through the pipe [-]
Re_p	Reynolds number of aerosol particle [-]
Re_λ	Turbulent Reynolds number [-]
SG	Specific Gravity [-]
$S_{\bar{r}}$	Standard deviation [-]
Stk	Stokes number [-]
t	Time [s], or coverage factor to calculate precision limit
t_0	The starting time [s]
T	Temperature [k]
Tr	Transmitted light for a sample in the spectrophotometer [-]
u	Velocity component in the r-direction, or the x-direction [m/s]
u_e	Eddy characteristic velocity scale [m/s]

U	Total uncertainty [-]; or instant velocity [m/s]; also used to denote the relative velocity between the sphere and the fluid [m/s]
$\bar{V}$	Velocity of air [m/s]
v	Velocity component in the α -direction, or the y-direction [m/s]
V	Area average speed of air. Also used to denote volume occupied by particles and fluid [m/s]
V_p	Volume of a single particle [m ³]
Vol	Volume of wash solution [m ³]
w	Velocity component in the θ -direction, or the z-direction [m/s]
X, Y, Z	Rectangular coordinates [-]

Greek

β	Bias errors [-]
δ	Total error [-]
ρ	Density [kg/m ³]
$\rho_{atmosphere}$	Atmospheric air density [kg/m ³]
μ	Viscosity of air [Pa·s]
μ_T	Turbulence viscosity [Pa·s]
∇^2	Laplace operator [-]
∇	Gradient operator [-]
α	Angular coordinate around the pipe cross-section [-]
ν	kinematic viscosity of the fluid [m ² /s]
λ	Density ratio [-]
τ	Time scale [s]
τ_e	Time scale of eddies or turn-over time of large eddy [s]
τ_L	Lagrangian fluid time scale [s]
τ_p	Particle response time or particle relaxation time [s]
τ_K	Kolmogorov time scale [s]

τ_{xy}	Stress on a fluid element, the first subscript referring to the face, the second to the direction [s]
Ω	Absolute value of vorticity [-]
Φ_p	Volume fraction of particles [-]
$\Phi, \Phi_1, \Phi_2,$ $\beta, \beta', \alpha,$ σ, σ'	Constants in the turbulence model [-]
ε	Dissipation rate of turbulence kinetic energy [m ² /s ³]; also used as precision error [-]
ω	Turbulent frequency
Γ	Velocity gradient [1/s]

Subscripts

<i>f</i>	Fluid or filter
<i>p</i>	Particle
<i>rel</i>	Particle relative to the flow field
<i>e</i>	Eddy
<i>x,y,z</i>	x,y,z components
<i>xy, etc</i>	On the x-component face, pointing in the y-direction, etc.
<i>0,1,2</i>	Fluid 0, 1, or 2 (Appendix A)
<i>G</i>	Relative to the gravity
<i>B</i>	Relative to the body
<i>F</i>	Fluid
<i>m</i>	Time mean values
<i>model</i>	Model
<i>n</i>	Nasal cavity model
<i>rms</i>	Root mean square
<i>t</i>	Turbulent
<i>real</i>	Real
<i>w</i>	Water

Superscripts

- ' Turbulent fluctuations
- (0) Undisturbed flow field
- (1) Perturbation of the flow field
- (2) Perturbed flow field

Chapter 1: Introduction

Aerosols, defined as suspensions of fine solid particles or liquid droplets in a gas, are very common in our daily life. For example, they are present in smoke, oceanic haze, particulate and condensed forms of air pollution, and sprays. A subclass of dispersed particle-laden multiphase flows, research on aerosols is foundationally important to many engineering applications that are related to aerospace, atmospheric, mechanical, biological, chemical, civil, and/or nuclear systems.

The deposition and clearance of inhaled aerosol in the respiratory tract (nasal cavity, mouth-throat, larynx, and lung) are important to human health (Finlay, 2001). This issue continues to be an intense subject of research with specific applications such as prevention and control of respiratory diseases, as well as development of nasal drug delivery, which is the eventual target application of the present work. Nasal drug delivery is a promising alternative to oral and injection routes of medication administration. For example, diabetes is a medical condition in which the body does not produce or use insulin, leading to dangerously high levels of glucose in the blood. It is estimated that 20.8 million people in the United States have diabetes -- 7% of the total population (data from the American Diabetes Association). In 1995, 135 million people worldwide had diabetes and it is expected that this number will rise to at least 300 million by 2025 (Narayan et al., 2003). In the developed world, diabetes is the most significant cause of adult blindness in the non-elderly and the leading cause of non-traumatic amputation in adults. Diabetic nephropathy is the primary disease requiring renal dialysis in the United States (Petni et al., 2006). It can be painful and hard for most of the

patients with diabetes to tolerate the many daily needles required for glucose measurement and insulin injection. Needle-free insulin delivery is considered a highly desirable and promising approach, and provides rapid and sustainable absorption of insulin (Petni et al., 2006).

The research of airflow patterns and aerosol deposition within the human nasal cavity geometry is the foundation for improving fraction of nasal drug delivery. Also, nasal breathing is the normal mode of inhalation of ambient aerosols for most adults at low to moderate activity levels, and is the only normal mode of inhalation for young infants when they are at rest (Barry and O'Callaghan, 1997; Schuepp, 2004). To determine the amount of nasally inhaled aerosols deposited in the lungs, it is necessary to know the nasal-throat deposition fraction during nasal breathing (Morgan and Monticello, 1990; Subramaniam et al., 2003; Swift, 1981).

For researchers involved with inhaled aerosols in nasal drug delivery and transmission of environmental aerosols and airborne pathogens, the most important task is to make a predictive understanding of aerosol deposition in order to control aerosol deposition in the respiratory tract, to optimize therapeutic effects of pharmaceutical aerosols, or to minimize detrimental influences of unwanted aerosol particles.

The highly complex geometry of the human nasal cavity is not only an obstacle in the research of airflow patterns in nasal cavity and nasal drug delivery, but also raises significant challenges in clinical research in many related fields including nasal surgery (e.g. Adamson, 1987; O'Neil and Tolley, 1998; Rober et al., 1998; Saunders et al. 1999; Minn et al., 2002; Murry et al., 2003; Pang, 2005; Zhao et al., 2006), nasal toxicology (e.g. Yu et al., 1998; Kimbell et al., 2001; Overton et al., 2001; Bennett and Zeman,

2005; Roberts et al., 2006; Kimbell, 2006; Tian et al., 2007; Schroeter et al., 2008), risk assessment (e.g. Roush, 1979; Wang et al., 2003; Rhomberg and Lerandowski, 2006), disease diagnosis (e.g. Lenders and Pirsig, 1990; Raj et al., 2000; Kramer and Wray, 2000; Suzina et al., 2003; Davis and Eccles, 2004), and olfaction (e.g. Churchill et al., 2004; Damm et al., 2002; Zhao et al., 2004).

1.1 Nasal drug delivery

Traditionally, medication in the form of drops or aerosols has been delivered to the nasal cavity in the treatment of allergies and congestion. More recently, mainly due to developments in safer and better tolerated enhancers to improve medication absorption by the nasal mucosa, the nasal tract has been considered for the delivery of vaccines, insulin, and other medications to treat osteoporosis, blood disorders and migraine headaches (Illum, 2000). Several published work (e.g. Sarkar, 1992; Hussain, 1998; Illum, 2000) showed that nasal drug delivery can allow drugs that do not cross the blood brain barrier (BBB) to be delivered to the central nervous system (CNS), thus eliminating the need for systemic delivery and thereby reducing unwanted systemic side effects (Frey, 2002; Dwibhashyam and Nagappa, 2008). This method works because of the unique connection that the nerves involved in sensing odours and chemicals provide between the brain and the external environment (Illum, 2000).

Compared with other drug delivery methods such as intravenous (IV) infusion, oral and injection routes of delivery, nasal drug delivery has considerable advantages. Some

of these are as follows (Minn et al., 2002; Hussain, 1998; Mathison et al., 1998; Frey, 2002; Talegaonkar and Mishra, 2004):

- Nasal drug delivery is needle-free, pain-free and comfortable;
- The nasal mucosa has rich vasculature, with a highly permeable structure that enables easy accessibility to blood capillaries greatly enhancing drug absorption;
- Nasal drug delivery can bypass the blood brain barrier (BBB) and target the central nervous system (CNS), reducing systemic exposure and thus systemic side effects;
- Nasal drug delivery avoids the modification of the medical agent which is delivered;
- Nasal drug delivery circumvents the problem of degradation of peptide drugs to a certain extent; and
- Nasal drug delivery allows high, reliable bioavailability because of avoidance of destruction in the gastrointestinal tract, hepatic “first pass” elimination and gut wall metabolism.

Because of its considerable advantages, nasal drug delivery is widely used in many applications including delivery of protein therapeutic agents / macromolecules to the CNS, delivery of DNA plasmids to the CNS, and delivery of small molecules to the CNS (Illum, 2000; Mathison et al., 1998; Hussain et al., 1998, Patni *et al.*, 2006).

1.2 Nasal anatomy and respiratory physiology

To study the mechanism of nasal drug delivery, a brief description of the nasal physiology

is necessary. As an interface between the body and the external world and the first part of human respiratory system, the nose and associated structures perform very important functions concerned with (Marieb, 1995, Grothberg, 2001):

- (1) Conditioning inhaled air (warming and/or humidifying);
- (2) Filtering inhaled air and cleaning it of foreign matter;
- (3) Serving as a resonating chamber for speech; and
- (4) Housing the olfactory (smell) receptors.

While the human nasal cavity is highly variable among individuals, it does retain several key features. The nasal cavity is nominally symmetric and is separated into two distinct air passages by a vertical thin wall called the nasal septum. The top part of the nasal cavity is formed by bones and cartilage and is tent shaped. The floor of the nasal cavity is formed by the palate, which separates the nasal and oral cavities and extends horizontally toward the posterior of the skull. As shown in Figure 1.1a, there are three shelves on the lateral wall known as turbinates or conchae, which serve to increase the surface area exposed to the air, thus increasing heat and moisture exchange. The grooved space below each turbinate is referred to as a meatus. The turbinates and meatuses are each labelled superior, middle, or inferior (see Figure 1.1b).

In the nasal vestibules, the regions just after the nostrils, numerous filtering hair follicles and sebaceous glands are present (Rajagopal and Jerry, 2005). Nasal hairs, or vibrissae, consist of the usually small hairs that are in the nose, especially those near the nostrils. Biologically, the hairs act as a filter and keep dust and dirt out of the nasal passages. They also help to maintain humidity in the air passages by trapping humidity

during exhalation, which then re-evaporates during inhalation to humidify inhaled air (Marieb, 1995).

Figure 1.1 Anatomical illustration of the human nasal cavity of a sagittal plane cut (a) and sample coronal plane midway through the nasal cavity (b)

In the superior region of the nasal cavity, the walls are covered by olfactory mucosa. The remainder of the nose is lined with respiratory mucosa (containing ciliated epithelium, producing mucus and secreting sticky mucus containing lysozyme and antibacterial enzymes), which clears the cavity by moving contaminated mucus towards the pharynx (throat), where it is swallowed (Marieb, 1995). As a human breathes, inhaled air enters the nasal cavity from the nostril and passes through the narrowest portion of the nasal cavity, i.e. the nasal valve, which increases its speed (Fishman and Geiger, 1985; Fidone and Gonzalez, 1986). The air then expands and decelerates while flowing through the middle and posterior part of the nasal cavity, impinging and

circumventing the three turbinates, and potentially creating turbulence that promotes contact between the air and the mucosa. With this complex geometry, the nose filters, warms and humidifies the entering air.

Table 1.1 shows a fluid dynamic description of human respiration summarized by Tang et al., (2004). As reported by Bilgen et al. (1974) and Tang et al. (2004), during normal breathing, such as in relaxed, resting and sleeping conditions, the inhalation and exhalation flow rate is usually 7.5-12 L/min (or 125-200 mL/s) and the main flow features are periodic and laminar flow. In non-normal conditions, such as exertion, sickness (asthma, nasal polyp, heavy vibrissae, sneezing, etc.) and physical exercise, the inhalation and exhalation flow rate can reach approximately 12-38 L/min (200-625 mL/s) (Robert, 2001) and the main forms of flow include constriction flows, obstructed flows, extra mucus flows and turbulent flows. A higher flow rate, 150 L/min (2500 mL/s), can be reached for some specific conditions such as forced inhalation or extremely deep breathing (Hooper, 2001). In polluted environments (where air may contain inorganic, organic, and/or synthetic material dust as well as chemical gas) or during drug delivery, more complexity is added to the main flow features, and aerosol flows, free surface flows, permeation flow and biological reactions may be present.

Table 1.1 Fluid dynamic description of human respiration (as summarized by Tang *et al.*, 2004).

Breathing conditions		Behaviour & Symptoms	Related locations	Main flow features	Simulation approaches
1	Normal: -quiet -resting -sleeping	Inspiration Expiration Flow rate of 125-200 mL/s	a. nasal cavity b. larynx c. trachea d. bronchi	Periodic flow, Laminar flow, Gap flow, small deformation at the junction of b and c.	Sinusoidal velocity profiles, single phase approach
2	Abnormal: -exertion -sickness -physical exercise	-asthma -nasal polyp -heavy vibrissae -foreign-body -sneezing Flow rate of 200-700 mL/s		constriction flow, obstruction flow, extra mucus flow, high flow rate, turbulent flow, deformation at the conjunction of a to d.	single phase approach, multiphase approach, turbulent model free surface model, Fluid-Structure Interaction (FSI) approach,
		-morbid surface		excessive dry/secretion of the mucosal surface permeation flow	liquid film flow model specific boundary model porous media model
		-cough -snore -yawn	a-d. e. mouth	high flow rate with deformations and vibrations in c or d-e	FSI approach, acoustic approach
3	Drug delivery -inhale -collunarium	Therapy spray	a. nasal cavity b. larynx c. trachea d. bronchi	Aerosol flow, Droplet flow, Free surface flow, Permeation flow Biological reaction	Multiphase approach, FSI approach, Porous media model
4	Air pollution: - inorganic, organic, or synthetic material dust - chemical gas	Silicosis Asbestosis, Chronic obstructive Pulmonary disease			

1.3 Two-phase flow and mechanisms of particle deposition

Two-phase flow entails fluid dynamic motion of various phases. Particle components of a two-phase flow can be solid, liquid, or gas, while the surrounding fluid must be a liquid or a gas (Crowe, 2005). Two-phase flows can also be categorized by concentration. Volume fractions of 0.1% or even less lead to “sparse” flows, where particle concentrations are so low that both particle-particle interactions and the effect of particles on the surrounding fluid are negligible (Elgobashi, 1994, Crowe, 2005). In this case,

only the continuous-fluid affects particle motion, and the interaction between the particles and surrounding flow is called as one-way coupling. When the particle volume fractions are less than 10% and particles sizes are small compared to that of the overall domain, two-phase flows are considered “dispersed” (Loth, 2009). In this case, the changes in particles trajectories are dominated by their interaction with the surrounding fluid, and the particle motion is chiefly governed by particle inertia and the fluid dynamic surface forces (e.g., drag force) and body forces (primarily gravitational). This interaction is called two-way coupling. For volume fractions greater than 10%, flows are referred to as “dense” two-phase flows, where particle movement is dominated by particle-particle interactions, e.g. by collisions or contact mechanics (Elgobashi, 1994) and this regime is termed four-way coupling.

Research of particle-laden two-phase flow is fundamental to many engineering applications including energy systems (e.g. circulating fluidized beds), propulsion (e.g. rocket engines), atmospheric dispersion (e.g. models of the concentration distribution of micron and sub-micron sized solid and liquid particles in the atmosphere) and biological flows (e.g. particle motion in the blood stream and the body, nasal drug delivery), to list just a few. Table 1.2 summarizes common two-phase flows in various engineering systems (Loth, 2009).

Table 1.2 Two-phase flow in various engineering systems, summarized by Loth (2009)

Two-Phase Flows	Engineering Application
Solid particles in a gas	fluidized beds, solid rockets, particle separators, ventilation ducts
Liquid droplets in a gas	atmospheric analysis, liquid fuel sprays, nasal or oral drug delivery devices
Solid particles in a liquid	liquid filters, sedimentation, solidification, slurries
Gas bubbles in a liquid	naval vessels, bubble columns, molten metal baths, boilers

1.3.1 Particle Deposition

There are five basic mechanisms by which an aerosol particle can be deposited on a wall or a fibre (Hinds, 1982; Guha, 2008): inertial impaction, diffusion, gravitational settling, interception and electrostatic deposition. The most important mechanisms for inhalation particle deposition are inertial impaction, sedimentation, and diffusion (Hinds, 1982).

(1) Inertial impaction

Inertial impaction of a particle on a fibre (for examples, nasal hairs for inhaled particles) (or even an adjacent wall) occurs when a particle, due to its inertia, is incapable of adjusting quickly enough to the suddenly changing streamlines in the vicinity of a fibre and crosses those streamlines to hit the wall or the fibre. Inertial impaction is a major deposition mechanisms for aerosol particles bigger than $1\mu\text{m}$ (Tien and Ramarao, 2007). During inhalation, the directions of inhaled air change several times as it flows from the nose or mouth down through the branching airway system (Hinds, 1982). Each time the air changes direction, the suspended particles tend to keep moving in their original direction for short distance because of their inertia. When the particles diverge from the corresponding streamlines, some of them may impact on the airway surface, which leads to particle deposition.

(2) Diffusion

For small particles (less than $1\mu\text{m}$ in size), Brownian diffusion and turbulent diffusion are sufficiently important to greatly enhance the possibility of the particles hitting a fibre while traveling past it on a non-intercepting streamline (Friedlander and Johnstone 1957; McCoy and Hanratty 1977). This is most likely to occur in smaller

airways where distances are short and residence times are comparatively long. Diffusion is the predominant deposition mechanism for particles smaller than $0.5\ \mu\text{m}$ (Schulz et al., 2000), and is governed by geometric rather than aerodynamic size, which means the density of particle is not an important factor for this mechanism. Gehr and Heyder (2000) pointed out that since smaller particles tend to reside longer in the respiratory system, the probability of smaller particles hitting an airway surface by diffusion is increased.

(3) Gravitational settling

Gravitational setting (also called sedimentation) is the most important deposition mechanism in the smaller airways and the alveoli where airflow velocities are low and airway dimensions are small (Schulz et al., 2000). Since the driving force for deposition via this mechanism is due to gravity, sedimentation has its maximum removal effect in airways that are oriented horizontally. In contrast with diffusional transport, gravitational settling is significant for the deposition of particles larger than $0.5\ \mu\text{m}$ (Schulz et al., 2000). Also, the distance a particle settles within a given time increases with its density. For inhaled aerosol particles, the longer a particle remains in the respiratory airway, the larger the settling distance the particle can cover, and hence, the larger the probability that the particle can hit on the airway surface. Hygroscopic particles (particles that preferentially absorb water) grow as they pass through the water-saturated airways, and this increase in size favours deposition by sedimentation and impaction in the distal airway (Hinds, 1982).

(4) Interception

Particle deposition by interception occurs specifically when a particle follows a gas streamline that happens to come within one particle radius of the surface of a wall or a fibre. This mechanism is not very important in deposition of inhaled particles (Hinds, 1982). The probability of interception depends on the proximity of the gas streamline to the airway surface and on the ratio of particle size to airway diameter, which is usually small even in the smallest airways. Generally, interception is an important deposition mechanism only if the inertial impaction effect is negligible (Tien and Ramarao, 2007).

(5) Electrostatic attraction

Although most ambient aerosol particles are neutralized by air ions, many freshly generated particles often carry electrostatic charges which may affect their deposition. Highly charged particles are attracted to airway surfaces by the electrostatic image charges generated by the presence of these charged particles and thus, may have an enhanced deposition (Yu, 1985).

1.4 Focus of the current research

Aerosol particle distributions and deposition patterns in the nasal cavity are critical parameters affecting the fraction of nasal absorption. To optimize the delivery of therapeutic aerosols, a full understanding of airflow patterns and particle deposition patterns in the human nasal cavity is necessary through experimental (both *in vitro* and *in vivo*) and numerical studies. The deposition of particles in the nasal cavity is a function of particle size and respiratory patterns. The density, shape, and hygroscopicity of

particles, the pathological conditions in the nasal passage and the inhalation flow rate all influence the deposition of particles.

Although several previous researchers have investigated deposition of inhaled aerosols for both oral and nasal breathing during the past decades (e.g. Swift, 1991; Lennon et al., 1998; Cheng et al., 1988; Zwartz and Guilmette, 2001; Cheng et al., 2001; Janssens et al., 2001; Kelly et al., 2004; Garcia et al., 2009), to the author's knowledge, none have done so using a standardized geometry and very few attempts have been made to quantitatively characterize regional deposition of inhaled particles in the nasal cavity. One part of present work was to create a standardized three-dimensional geometry of the human nasal cavity representative of the general population that could be used for a variety of applications including research on nasal drug delivery and deposition. Although several reports related to the measurement of characteristic dimensions of the human nasal cavity and generation of human nasal cavity models have appeared in the literature (see detailed discussion in section 2.1), prior to the current work, the creation/construction of a median human nasal cavity geometry had not been attempted and accomplished.

Using the novel standardized human nasal cavity geometry, numerical simulations and experimental (*in vitro*) measurements of aerosol particle deposition patterns and airflow patterns were performed. Results from this work offer detailed information of aerosol particle deposition, including regional deposition patterns, which are important factors affecting the fraction of nasal absorption, and are important for advancing nasal drug delivery technology.

Specific goals of the research presented in this thesis were to:

1. Summarize geometric characteristics of the nasal cavities of 30 healthy adults by processing computed tomography (CT) scans offered by the Ottawa Hospital, Civic campus; develop an objective methodology for aligning, scaling, and averaging the associated 60 single individual nasal passages; and use this methodology to create a single, detailed, realistic, standardized geometry that could be considered as a standard human nasal cavity for *in vitro* aerosol deposition studies and numerical simulation;
2. Design a particle deposition apparatus and conduct experiments to measure total and regional particle deposition fraction using the standardized nasal geometry;
3. Simulate airflow patterns and particle deposition in the standardized human nasal cavity geometry using Reynolds Averaged Navier-Stokes equations/Eddy-interaction model (RANS/EIM) and standard Large Eddy Simulation (LES), to better understand the limits of applicability and accuracy of standard numerical methods (mostly available in commercial packages);
4. Investigate influences of particle size and air flow rate on particle deposition patterns;
5. Improve understanding of dispersed particle-laden flows within the geometrically complex human nasal cavity;
6. Investigate influences of nasal geometry (especially the size of nostril) on airflow patterns and particle deposition patterns.

1.5 Thesis Organization

The thesis consists of 8 chapters. Chapter 1 summarized the motivation, background and aims of current research. In Chapter 2, a literature review concerning airflow patterns and particle deposition fraction in human nasal cavity is presented. The construction of the “Civic-Carleton” novel standardized human nasal cavity geometry is described in Chapter 3. In Chapter 4 the experimental apparatus and method used to measure the total and regional particle deposition fraction in the novel standardized human nasal cavity are described. Chapter 5 presents the discussion of measured total and regional particle deposition fraction in the novel standardized human nasal cavity. Chapter 6 describes the numerical simulation methodology adopted in present research. In Chapter 7, grid convergence and sensitivity analyses are performed, and simulation results of total particle deposition as well as simulated airflow patterns in the standardized human nasal cavity are presented and discussed. Chapter 7 also discusses the numerical and experimental results of regional particle deposition fraction. Finally, conclusions are summarized in Chapter 8 along with recommendations for future work.

Chapter 2: Literature Review

A better understanding of deposition of inhaled aerosol within the complex human respiratory system (nasal cavity, oral cavity and respiratory tract) is important in developing pharmaceutical aerosols for drug delivery, as well as in preventing and controlling the health risks associated with environmental aerosols and bio-aerosols. Although several studies of deposition of inhaled aerosols for both oral and nasal breathing have been conducted during the past few decades, for the most part these have used specific nasal geometries and in many cases these have been limited by a lack of a standardized or generalized geometry representative of the broader population. In this chapter, a brief review of previous investigations of human nasal cavity geometry, airflow patterns, and particle deposition fraction is presented.

2.1 Previous Measurements of characteristic dimensions in human nasal cavities

Many attempts have been made to measure characteristic dimensions of the human nasal cavity to create a realistic human nasal cavity 3D model. Data on characteristic dimensions of the human nasal cavity (cross-sectional area, surface area, volume and nostril shape) is the foundation of experimental and numerical studies of airflow patterns and particle deposition patterns.

As discussed in Section 1.2, the human nasal cavity is highly complex and variable among individuals, which not only makes the study of particle deposition in nasal cavity

difficult, but also raises significant challenges in clinical research in many related fields. Fortunately, advanced technology such as computed tomography (CT), acoustic rhinometry (AR) and magnetic resonance imaging (MRI) make it possible to gather detailed information on the dimensions of the human nasal cavity. Table 2.1 summarizes the measurements taken in several previous studies along with number of subjects and techniques used.

Table 2.1 Summarized measurements of characteristic dimensions of human nasal cavities

Researchers and year	Number, gender (M/F) and age of subjects	Method	Reported Measurement Data	Focus of paper
Hilberg et al., 1989	6, 3/3, 22~55 years	AR	Cross-sectional area as a function of distance for both left and right nasal cavities	Assessed AR technique for measuring cross sectional area of the nasal cavity as a function of the distance from the nostril
Min et al., 1995	30, 22/8, 20~62 years	AR and CT scans	Cross-sectional area as a function of distance for both left and right nasal cavities	Evaluated the validity and characteristics of AR tests compared with the results obtained from CT scans
Swift and Kesavanathan, 1996	1, 1/0, N/A	<i>In vivo</i> casting	Cross-sectional area, perimeter, and hydraulic diameters of 11 cross sections	Used fibrous filter theory to determine the deposition fraction in nasal cavity
Cheng, Y. S. et al., 1996	4, 4/0, 36~57 years	MRI	Cross-sectional area, total surface area, and perimeter of cross sections	Experiments on deposition of ultrafine particles in human nasal cavity and its relationship to airway geometry
Cheng, K. H. et al., 1996	10, 10/0, 24~58 years	MRI and AR	Minimum cross-sectional area, surface area, and defined "shape complexity"	Deposition fraction in terms of nasal shape parameters
Corey et al., 1997	5, 3/2, N/A	AR and MRI	Cross-sectional area and volume as a function of distance	Determine accuracy of AR as a technique in assessing nasal CSAs and volumes by comparing with MRI
Kesavanathan and Swift, 1998	10, 7/3, 23~60 years	AR	Nostril shape (characteristic dimensions)	Effect of particle size, flow rate, nostril shape and nasal passage geometry on nasal particle deposition fraction
Terheyden et al. 2000	6, 3/3, 22~55 years	CT scans and AR	Comparison of CSA-distance curve using CT scans and AR	Validate the AR technique against CT scanning

2.1.1 Measurements Using Acoustic rhinometry

Acoustic rhinometry (AR) is based on reflections of an acoustic pulse applied to the nostrils. From the reflected wave, the serial distribution of impedance can be calculated as a function of traveling time (Jackson *et al.*, 1977). Because acoustic impedance depends on the cross-sectional area, the result is presented as a serial distribution of cross sections of an acoustic system equivalent to the acoustic properties of the nose (Jackson *et al.*, 1977). This method has many advantages: it is noninvasive, it requires little cooperation of the subject, and it is applicable in small children (Buenting *et al.*, 1994). Thus, AR has been widely used to make *in vivo* cross-sectional measurements of the human trachea and the lower airways (Jackson *et al.*, 1977; Fouke and Strohl, 1987). In 1989, the method was introduced for assessment of the patency of the nose (Hilberg *et al.*, 1989).

Several investigations have been performed in the last decades to measure basic characteristic dimensions of the human nasal cavity using AR including Cheng KH *et al.*, (1996); Corey *et al.*, (1997); Hilberg *et al.*, (1989); Kesavanathan and Swift (1998); Min and Jang (1995); and Terheyden *et al.*, (2000). Kesavanathan and Swift (1998) measured the characteristic dimensions of the nostrils of ten healthy Asian and European American subjects aged 23-60 years using AR. Three nostril shape measurements were taken: the major axis of the nostril cross-section (the length of the nostril), the minor axis of the nostril cross-section (the width of the nostril), and the angle of the major axis with the base of the nose. Several of the other studies listed (e.g Hilberg *et al.*, 1989; Min and Jang, 1995; Reber, 1998; Terheyden *et al.*, 2000; Damm *et al.*, 2002;) were primarily

concerned with demonstrating the acoustic rhinometry technique for estimating flow cross-sectional areas and comparing its accuracy with more precise MRI and CT measurements. As noted by Terheyden et al. (2000), AR is better used as diagnostic tool for the anterior parts of the nose, since the measurement accuracy of AR in the posterior nasal cavity is unsatisfactory.

2.1.2 Nasal Cavity Measurements using Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) is a medical imaging method using X-rays to obtain images, and is widely used in the medical field (to create cross-sectional pictures of the body). Magnetic resonance imaging (MRI) is similar to CT but uses non-ionizing radio frequency signals to acquire images and can provide much greater contrast between the different soft tissues of the body than CT. Compared with CT, MRI is a relatively new technology whose first image was published in 1973 (Lauterbur, 1973; Hinshaw et al., 1973), and the first published studies performed on the human body appeared in 1977 (Damadian et al., 1977).

Rapid developments in medical imaging (CT and MRI scanning) coupled with computer science have made it possible to obtain detailed geometric information of nasal cavity (Min and Jang, 1995; Cheng KH et al., 1996; Corey et al., 1997; Terheyden et al., 2000; Cheng YS et al., 2003).

As shown in Figure 2.1, published measured results of cross sectional areas of the human nasal cavity using AR, CT or MRI scanning span a wide range, indicating the

non-negligible individual differences among human nasal geometries. This illustrates the importance of generating a standardized 3D human nasal cavity which can eliminate the significant individual differences while representing the general population. In present work, CT data were used to create a standardized 3D human nasal cavity model. Detailed analysis and comparison of the dimensions of the standardized 3D human nasal cavity model with previous data will be presented in Chapter 3.

Figure 2.1 Cross-sectional areas of nasal models (green curve) derived from published data of CT scans and MRI scans

2.2 Published 3D human nasal cavity models

Several realistic 3D models of the human nasal cavity have been generated using magnetic resonance imaging (MRI) (Swift 1991; Schreck et al., 1993; Guilmette and Gagliano, 1994; Zwartz and Guilmette, 1999; Shanley et al., 2008; Garcia et al., 2009) and computed tomography (CT) (Lennon, 1998; Kelly et al., 2000, Inthavong et al., 2006). These are summarized in Table 2.2.

It can be seen from Table 2.2 that, there are only nine different subjects (7 males/2 females) were used to generate replica or 3D models of nasal cavities. Sometimes, a set of MRI or CT scan was used by different researchers to generate physical 3D replicas using different manufacturing methods. For example, six replicas were generated to perform particle deposition experiments using the same set of MRI scans of nasal cavity of a 53-year-old non-smoking Caucasian male (Swift, 1991; Guilmette et al., 1994; Zwartz & Guilmette, 2001; Kelly et al., 2004; Garcia et al., 2009), and Shi et al. also used this set of MRI scans to generate 3D model to simulate inertial particle transport and deposition in human nasal cavities.

Among these nine subjects, age information of four of them was provided (25/25/53/59-year-old), and all these four subjects were healthy male. For body mass, information of five out of nine subjects was provided (Swift, 1991; Inthanvong et al., 2006; Replica 2, 3, and 4 of Garcia et al., 2009): varied from 55.3 kg to 74 kg. About gender information, the ratio of male to female was seven to two. Only four subjects had specific ethnic information: two Caucasian (Swift, 1991; Guilmette & Gagliano, 1994) and two Asian (Kim & Chung, 2003; Inthanvong et al., 2006), who were all male.

In summary, even though several 3D nasal cavity models have been generated and have been used by different researchers to perform experiments and numerical simulations, none of them can be used as a median or standardized model to represent the general population because all previous models were generated from data source of single subject. Another limitation of previous subjects is lacking of physiological and ethnic diversity.

Table 2.2 Summary of 3D human nasal cavity models

Researchers and year	Data source and information of subjects	Scan resolution	Outlining method	Manufacturing methods	Scale ratio	Manufacturing resolution (mm)	Measurements or simulations	Use in other studies
Swift, 1991	MRI, a 53-year-old non-smoking Caucasian male (73 kg)	3 mm (coronal)	Traced by hand	Carving coronal plates by hand with high-speed cutting tool	1	N/A	Experiments on particle deposition	Experiments (Guilmette et al., 1994; Zwartz & Guilmette, 2001; Kelly et al., 2004; Garcia et al., 2009) Simulations (Shi et al., 2007)
Guilmette et al., 1994	Same as Swift, 1991	3 mm (coronal)	Digitized using CAD software	Computerized milling machine	1	1.5 (coronal) 0.02 (lateral)	Experiments on particle deposition	N/A
Zwartz & Guilmette, 2001	Same as Swift, 1991	3 mm (coronal)	Digitized using CAD software	Computerized milling machine	1	1.5 (coronal) 0.02 (lateral)	Experiments on particle deposition	N/A
Kelly et al., 2004 SLA replica	Same as Swift, 1991	3 mm (coronal)	Digitized using CAD software	Stereolithography SLA 7000 (3D Systems, Inc.)	1	0.25 (coronal) 0.102 (lateral)	Experiments on particle deposition	N/A
Kelly et al., 2004 Viper replica	Same as Swift, 1991	3 mm (coronal)	Digitized using CAD software	Stereolithography Viper Si2 machine (3D Systems, Inc.)	1	0.075 (coronal) 0.051 (lateral)	Experiments on particle deposition	N/A
Garcia et al., 2009 Replica 1	Same as Swift, 1991	3 mm (coronal)	Digitized using CAD software	Stereolithography Viper Si2 machine (3D Systems, Inc.)	1	0.075 (coronal) 0.051 (lateral)	Experiments on particle deposition	N/A
Guilmette & Gagliano, 1994	MRI, a 59-year-old non-smoking Caucasian male	3 mm (coronal)	Digitized using CAD software	Computerized milling machine	1	0.5 (coronal) 0.02 (lateral)	Experiments on particle deposition	Experiments (Zwartz & Guilmette, 1999)
Zwartz & Guilmette, 1999	Same as Guilmette & Gagliano, 1994	3 mm (coronal)	Digitized using CAD software	Computerized milling machine	1	0.5 (coronal) 0.02 (lateral)	Experiments on particle deposition	N/A
Kelly et al., 2000	CT scans, a healthy 25-year-old man	1-5 mm (coronal)	Used IDEAS Master Series solid modeling package	3D printer (Z Corporation) and curing clear silicon (Dow Corning)	2	N/A	PIV experiments (Velocity)	Experiments (Hopkins et al., 2000) Simulations (Liu et al., 2007)
Hopkins et al., 2000	Same as Kelly et al., 2000	1-5 mm (coronal)	Used IDEAS Master Series solid modeling package	3D printer (Z Corporation) and curing clear silicon (Dow Corning)	2	N/A	PIV experiments (Velocity) Velocity	N/A

Kim & Chung, 2003	CT scans, Korean adults with and without adenoid vegetation	N/A	N/A	3D printer (Z Corporation) and curing clear silicon	1	N/A	PIV experiments (Velocity)Velocity	Experiments (Kim & Chung, 2004; Kim & Haw, 2004)
Inthanvong et al., 2006	CT scans of a 25-year-old healthy, non-smoking Asian male (73 kg, 173 cm)	1-5 mm (coronal)	3D modeling program GAMBIT	NA	1	N/A	Simulation on particle deposition	Simulations (Tian et al., 2007)
Shanley et al., 2008	MRI scans of an anonymous, healthy, adult male human subject	1-5 mm (coronal)	3D modeling program GAMBIT	NA	1	N/A	Simulation on particle deposition	N/A
Garcia et al., 2009 Replica 2, 3, and 4	MRI scans of three healthy subjects (2 females and one male)	3 mm (coronal)	Digitized using CAD software	Stereolithography Viper Si2 machine (3D Systems, Inc.)	1	0.075 (coronal) 0.051 (lateral)	Experiments on particle depositionParticle deposition	N/A

2.2.1 Methods of Manufacturing Nasal Cavity Replicas

As summarized in Table 2.2, there are several ways to manufacture replicas of nasal cavities from 3D nasal cavity models: assembly from coronal planes carved by hand; manufacture using different rapid prototyping technologies (sometimes combined with curing clear silicon) such as 3D printer, stereolithography (SL) and so on.

Swift (1991) generated a replica using MRI scans of the nose of a healthy, 53-year-old non-smoking Caucasian male (73 kg mass, 173 cm height). Swift's replica was assembled from a number of 3-mm thick plastic coronal elements carved by hand with a high-speed cutting tool whose diameter or size was unspecified. The outlines of the airway on the plastic elements were traced on each side of the junction of two elements and the elements were cut to follow the transition from one image to the next.

Schreck et al. (1993) constructed a physical nasal model by processing the internal anatomy of the airways obtained from magnetic resonance images (MRI) of the head and neck of one healthy adult subject. Twenty-seven Plexiglas (clear plastic) plates with a 12 mm thickness were cut using three times enlarged digitized coronal planes (spaced in 4 mm increments before enlargement) of the nasal airways. After cutting and polishing, the plates were assembled together to form a three times scaled single nasal cavity model of the left passage, which can be seen in Figure 2.2.

Guilmette and Gagliano (1994) described a method to create 3D physical human nasal cavity models from MRI data. The subject of their study was a 59-year-old healthy male non-smoker. Two models were generated, one containing the region from the tip of

the nostril to the posterior pharynx, and one excluding the olfactory region. Three dimensional lofted surfaces which described the nasal airways were created using CAD software and airway perimeter coordinates were obtained from the MRI scans. Then seventy 1.5-mm-thick black acrylic plates containing the airways were cut out using a computer-controlled micromilling machine using a 0.5 mm end. This manufacturing method had the advantages of accuracy and reproducibility compared with Swift's method. Zwartz and Guilmette (1999) modified the model created by Guilmette and Gagliano (1994) to generate a third model, by replacing the segments containing the olfactory region. Zwartz and Guilmette (2001) also use this method to construct two nasal cavity replicas based on the same MRI scans used by Swift (1991). One of the replicas did not contain the entire olfactory region and the other one included a 9% larger olfactory volume.

Figure 2.2 Side view of physical nasal cavity model created by Schreck et al., (1993)

Hopkins et al. (2000) established a procedure for constructing a transparent rectangular box containing a model of the nasal cavity for PIV measurement by combining the rapid prototyping (RP) and the curing of clear silicone. Kim and Son

(2003) improved the procedure for producing a better cavity model with high-resolution computerized tomography (CT) scan data and surface rendering and extended this work to deal with airflow in an abnormal nasal cavity with adenoid vegetation and asymmetry.

Among a large number of available rapid prototyping technologies in the marketplace stereolithography is widely used to build nasal cavity replicas. The advantages of Stereolithography method are that it is convenient to produce physical replicas of complex geometries and it has improved accuracy compared to other means such as hand carving.

Different manufacturing methods have different effects on the nasal replica, such as the surface roughness. As a result, the measured results (velocity or particle deposition fraction) using replicas manufactured by different methods would be influenced (Kelly et al., 2004). Kelly et al. (2004) created two physical models from the same MRI scans of Swift (1991) using stereolithography (SL), and then measured the inertial particle deposition fraction of these two replicas. One of the models was manufactured by Accelerated Technologies, Inc. (ATI, Austin, TX, USA) using SLA 7000 (3D System, INC., Valencia, CA, USA), and thus was referred as the SLA replica. The other one was referred as Viper replica, which was manufactured using a Viper Si2 machine (3D System, INC.). Kelly et al. (2004) found that their data showed lower deposition fraction when compared with other deposition results of previous researchers in nasal replicas created from the same set of MRI scans. Conclusion was drawn that certain part of the differences in deposition fraction can be attributed to differences in surface roughness resulted from different methods used to manufacture the replicas.

In summary, modern imaging technology such as CT, magnetic resonance imaging MRI along with the unprecedented development of CAD solid modeling technology make it possible to gather detailed anatomic information of the human nasal cavity and create 3D human nasal cavity models. Advanced manufacturing technology including Rapid Prototyping (i.e., Stereolithography etc.) offer several ways to build physical replicas of human nasal cavity models from 3D models stored in an electronic format, and thus facilitate investigate particle deposition and airflow patterns in human nasal cavity experimentally and numerically.

For this present application, the replica of standardized human nasal cavity model was produced using Soluble Support Technology 1200es Dimension 3D Printer (Stratasys, Inc., Eden Prairie, USA). The minimum layer thickness of the Dimension 3D printer was 0.25 mm (0.010 inches). The details about the generation of the standardized human nasal cavity model and the construction of the physical replica of it will be provided in Chapter 3 and Chapter 4.

2.3 Experimental studies of airflow patterns and particle deposition in human nasal cavities

2.3.1 Experimental studies of nasal airflow

Detailed knowledge of airflow patterns in the human nasal cavity is the foundation of understanding the physiological and pathological aspects of nasal breathing and patterns

of particle transportation and deposition in the nasal cavity. Several studies (e.g. Swift and Proctor, 1977; Girardin et al., 1983; Hahn et al., 1993; Schreck et al., 1993; Park et al., 1997; Kelly et al., 2000; Hopkins et al., 2000; Doorly et al. 2008) have utilized physical models of the nasal cavity in an effort to understand the relationship between nasal anatomy and the distribution of inhaled and exhaled airflow.

The highly complex geometry and compact size of nasal cavity makes the investigation of nasal airflow patterns difficult and challenging. There are two ways to solve the problem of measurement of airflow field in the human nasal cavity (as well as in the oral cavity and trachea). The first approach is to use an N times ($N \geq 2$) scaled nasal cavity model (Hahn et al., 1993; Schreck et al., 1993; Park et al., 1997; Kelly et al., 2000). The second approach is to build a transparent colourless model with an index-matched fluid (usually is optimal glycerol /water) and use standard PIV imaging and laser delivery system, as reported by Hopkins et al. (2000) and Doorly et al. (2008). These two approaches can be adopted together or separately to facilitate the measurement of complex flow field in human nasal cavity.

Adoption of these two approaches raises an important issue of similitude, i.e., the measurements must satisfy following criteria: Geometric similarity, Kinematic similarity and Dynamic similarity (see Kline, 1986 for more details about the similitude in the engineering measurements). The values of geometric dimensions, velocity of fluid, flow rates, pressure losses and time scales obtained using scaled models must be rescaled to real quantities.

Reynolds number matching is usually used to solve the problem (Hahn et al., 1993; Schreck et al., 1993; Park et al., 1997; Kelly et al., 2000), which means the Reynolds

Number in model must be equal to those of real air breathing condition to assure the dynamic similarity.

$$\text{Re} = \frac{UL}{\nu} = \text{constant} \quad (2.1)$$

Thus, the relation between measured and real values can be obtained using:

$$\frac{U_{\text{real}}}{U_{\text{measured}}} = \frac{L_{\text{model}}}{L_{\text{real}}} \frac{\nu_{\text{real}}}{\nu_{\text{model}}} = \frac{\xi}{N} \quad (2.2)$$

$$\frac{\dot{Q}_{\text{real}}}{\dot{Q}_{\text{measured}}} = \frac{U_{\text{real}}}{U_{\text{measured}}} \frac{L_{\text{real}}^2}{L_{\text{model}}^2} = \frac{\xi}{N} \frac{1}{N^2} = \frac{\xi}{N^3} \quad (2.3)$$

in which, U is velocity, $\dot{Q}$ is the flowrate, the N is the times of the scaled model (also called length scale $L_{\text{model}}/L_{\text{real}}$), ξ is the viscosity ratio ($\nu_{\text{model}}/\nu_{\text{real}}$).

If not stated otherwise, the values of the measurements (such as velocities, flowrates etc.) of previous researchers are all real values (physiological values) rather than model quantities (measured values).

Swift and Proctor (1977) performed the first quantitative *in vitro* velocity measurements. They measured the velocity of the air in the fluid field by inserting a miniature Pitot device into the flow passage of a nasal cavity model, which was made from a nasal cast of a cadaver. The flow was reported to be laminar at a flow rate of 125 mL/s. Turbulent flow was detected downstream of the nasal valve at a flow rate of 208 mL/s.

Kelly et al. (2000) noted several limitations for experimental study of airflow patterns in the nasal cavity using Pitot tubes with models from cadavers. These included issues associated with the approximate geometry due to both the flat septum and

variations between cadavers and live subjects that result from post-mortem shrinkage of tissue, the invasive nature of the Pitot device, which may deflect the air stream, resulting in a biased total pressure reading, and the small size of the cast model.

In order to solve the problem related to the small size of the cast model, Hahn et al. (1993) constructed a 20 times replica of a nasal cavity from computerized axial tomography (CAT) scans spaced in 2 mm increments from the nostril of the nose to the beginning of the nasopharynx. Pointwise velocity measurements, made in five planes throughout the model with a hotfilm anemometer, indicated that the flow was laminar at flow rates up to around 200 mL/s (e.g. 12 L/min). It was found that ~50% of inhaled air flows through the combined middle and inferior airways, and ~14% flows through the olfactory region at all flow rates studied.

Additionally, experimental studies on human nasal airflow patterns have been conducted using laser Doppler velocimetry (LDV) (Girardin et al., 1983). There are several advantages in using LDV to study human nasal airflow patterns, among which the most important one is that it allows the statistical averages of mean velocity and turbulence intensity to be determined. Due to the highly complex airflow patterns in the nasal cavity, as well as its three-dimensionality, high spatial gradients, and turbulence, the measurements of airflow patterns using point measurement techniques such as hotwire anemometry and LDV are difficult, expensive and impractical. These measurement techniques require that the particle density be sufficiently large for a reasonable data rate, and they require thousands of individual measurements to resolve the flow (Heenan et al., 2003).

In contrast, particle image velocimetry (PIV) is a powerful technique to measure fluid velocities, and is able to determine the instantaneous flow field over two- or three-dimensional domains. Park et al. (1997) were the first to use a two-dimensional measurement technique, digital particle image velocimetry (DPIV), to study nasal airflow patterns. A 33 times scaled nasal replica was generated from approximately nine coronal slices of anatomic data (from nostril to nasopharynx). Their results showed a noteworthy portion of the high-velocity flow occurred in the olfactory region. Their work was limited because the resolution of anatomic data used for their model was not high enough, and because vector plots in five sub-locations of each plane, forming the global velocity field, merged into others.

Kelly et al. (2000) used particle image velocimetry to determine two-dimensional instantaneous velocity vector fields in parallel planes throughout a two-times scaled model of a right human nasal cavity, and used a steady flow rate of 125 mL/s for inhaled air. The model adopted in their research was fabricated from 26 CT scans, using rapid prototyping techniques. The vector plots of measured results show that the flow was laminar and the highest velocities were detected at the nasal valve and along the floor of the nasal cavity in the inferior airway. The nasal valve has the smallest cross-sectional area in the nasal cavity, and thus there is high-velocity flow in that region. The relatively low flow in the olfactory region appears to protect the olfactory bulb from particulate pollutants. Low flows were also observed in the nasal meatuses. Comparison of sequentially recorded data suggests a steady flow.

Hopkins et al. (2000) performed PIV measurement using a nasal passage model made of clear silicone. Their measurements showed that an eddy can be seen in the

region just posterior to the nasal valve. They conjectured that this flow structure was a result of the adverse pressure gradient that is caused by the abrupt expansion in cross-sectional area in this region.

2.3.2 Experimental study of particle deposition in the airway passages

The deposition occurring within the human upper respiratory system has been a primary topic of interest for decades (Prattle, 1961; Johnston and Schroter, 1979; Chan et al., 1980; Kim and Iglesias, 1989; and Cohen and Asgharian, 1990, Lennon et al., 1998). The nasal cavity region has received particular attention (e.g. Heyder and Rudolf, 1977; Itoh et al., 1985; Heyder et al., 1986; and Cheng et al., 1988, Etherington et al., 1998) because of its highly complex geometry and important function in nasal drug delivery. Most information about particle deposition in the various human airway passages has been obtained through experimental work. In general, experimental measurements of deposition fraction in anatomical airways can either be conducted *in vitro* (using replicas) or *in vivo* (measurements directly on live patients).

2.3.2.1 In-vivo experimental studies of nasal particle deposition fraction

In typical *in vivo* measurements of nasal particle deposition, the aerosol concentration is measured before it is inhaled into the nasal cavity and after it is exhaled through the mouth (Pattle 1961; Hounam et al., 1969; Heyder and Rudolf, 1977; Stahlhofen et al., 1989; Cheng et al., 1996; Swift and Strong, 1996; Kesavanathan and Swift, 1998). As

shown in Figure 2.3, Pattle (1961) performed *in vivo* particle deposition experiments on a human subject, and results showed that the human nasal cavity particle deposition fraction can be represented as a unique function of the impaction parameter, $d_a^2 Q$. The data can be fitted with the following equation:

$$DF = 1 - \exp(-a'd_a^2 Q) \quad (2.4)$$

where d_a is the aerodynamic diameter, Q is the air flow rate in L/min, and $a' = 0.00241 \pm 0.002$ (*mean $\pm$ SEM*) with $r^2 = 0.94$, indicating a good fit.

Figure 2.3 Deposition fraction in human nasal cavity illustrated as a function of impaction parameter for an adult human volunteer (Pattle, 1961)

Similarly, inspiratory nasal deposition data for three subjects in a study by Hounam et al. (1969) and mean values of deposition measurements of six subjects by Landahl and Black (1947) could also be fitted by the same expression. Heyder and Rudolf (1977) measured both inspiratory and expiratory nasal deposition data in four adult male

subjects. All data from the four subjects showed that the inspiratory and expiratory nasal depositions were not statistically different (data not shown). This analysis indicates that the assumption of equal nasal deposition fraction for the inspiratory and expiratory flows used in most lung deposition models is reasonable.

Cheng (2003) summarized and analyzed available *in vivo* data in human volunteers of Landahl and Black (1947), Pattle (1961), Hounam et al. (1969), Giacomelli-Maltoni et al. (1972), and Heyder and Rudolf (1977). Cheng assumed that the airway dimensions cause the variability in the nasal deposition values, and he proposed Equation 2.5 as the correct mathematical expression for impaction deposition:

$$DF = 1 - \exp(-110Stk). \quad (2.5)$$

where $Stk = \rho^{0.5} d_a^2 Q / 18 \rho A_{\min}^{1.5}$, is the dimensionless Stokes number. The corresponding value of the minimum cross-sectional area in the nasal airway for each subject can be calculated using Equation 2.6:

$$A_{\min} = \left(\frac{0.00982}{\alpha'} \right)^{2/3} \quad (2.6)$$

Values of $A_{\min}$ for the eight subjects (one by Landahl and Black, 1947; four by Heyder and Rudolf, 1977; three by Hounam et al. 1971) ranged from 1.11–3.90 cm². The value of $A_{\min}$ corresponding to the mean value of $\alpha' = 0.00390$ was 2.11 cm².

Cheng et al. (1996) reported measurements of the nasal airway dimensions for 10 adult male volunteers using MRI scans. The value of $A_{\min}$ ranged from 1.28–3.10 cm² with a mean value of 2.08 cm². The calculated values of $A_{\min}$ from this analysis of deposition data are in approximately the same range, indicating that Cheng et al.'s (1996) values were reasonable.

As illustrated in Figure 2.4, Cheng (2003) summarized previous *in vivo* nasal deposition data using the same mathematical expression originally proposed by Pattle (1961) $DF = 1 - \exp(-a'd_a^2Q)$. The centre curve is for a mean value of 0.00309 ($A_{\min} = 2.16 \text{ cm}^2$) and the curves for the upper and lower bounds correspond to 0.00839 ($A_{\min} = 1.11 \text{ cm}^2$) and 0.00128 ($A_{\min} = 3.90 \text{ cm}^2$), respectively. The three curves summarized by Cheng (2003) represent an estimate under experimental conditions and can be used as a comparison standard for nasal cavity deposition.

Figure 2.4 Summary of nasal deposition fraction as a function of impaction parameter in human volunteers (after Cheng, 2003)

In recent nasal particle deposition research, *in vivo* studies using scintigraphy (radiolabeled aerosol + gamma camera) have been widely adopted, and several authors

have performed qualitative studies of *in vivo* nasal deposition using radiolabelled particles (see Suman et al., 1999; Giroux, 2005). Figure 2.5 shows the *in vivo* controlled dispersion particle deposition acquired using scintigraphy by Giroux in 2005, which provided visual particle distribution patterns using passive-diffusion nebulizers and nasal spray pumps. However, Giroux (2005) did not provided any quantitative analysis of total or regional particle deposition fraction.

Figure 2.5 Particle deposition in the nasal cavity using an *in vivo* scintigraphy method (left: using passive nebulizer; right: using nasal spray pump (Giroux, 2005))

2.3.2.2 In vitro experimental studies on nasal particle deposition fraction

In vivo studies on humans are limited by health and ethical issues since relatively large amounts of radioactivity are required to measure deposition in different nasal regions. To avoid high-dose radiation exposure, as well as to obtain more reproducible results, *in vitro* experiments, using artificial nasal cavities (nasal casts or replicas of nasal airways), have been used to complement difficult and expensive *in vivo* studies for decades. Apart from safety, there are several advantages of measuring particle deposition fraction using a human nasal cavity model (Zwartz and Guilmette, 2001). First, advanced manufacturing technology makes it possible to build an accurate nasal airway model with features such as a vestibule, nasal valve, olfactory region, turbinates and nasopharynx regions. In

addition, all parameters (i.e. inhalation flow rate, particle size, particle type), which may influence the nasal particle deposition, can be controlled and measured independently and systematically. This makes it easy and convenient to determine how these parameters affect the total and regional particle deposition fraction.

In *in vitro* experiments, particles were usually drawn into the model using a vacuum pump that produces a constant flow rather than cyclic flow patterns or realistic human breathing. Several *in vitro* measurements have been published including those by Swift (1991), Gradon and Podgorski (1992), Lennon et al. (1998), Cheng et al. (1998), Zwartz and Guilmette (2001), Cheng et al. (2001), Janssens et al. (1998), Kelly et al. (2004), and Garcia et al. (2009), as summarized in Figure 2.6 together with the semi-empirical fit line of in-vivo data summarized by Cheng (2003).

Except for the data from Swift (1991), which were obtained using a hand-carved replica, all of the previous *in vitro* data follow a similar trend, which falls below the summary *in vivo* curve of Cheng (2003). The difference between *in vitro* and *in vivo* measurements is not unexpected because the principles of the two measuring methods are different (a more detailed discussion of this will be presented in Chapter 5 with present *in vitro* measured results in the standardized human nasal cavity model).

In Figure 2.6, all of the data shown in blue were obtained by a variety of researchers using geometries manufactured from the same set of MRI scans for a single human subject originally reported by Swift (1991). These include the SLA and Viper models of Kelly et al. (2004), the first model of Garcia et al. (2009), and the models of Zwartz and Guilmette (2001), Cheng et al. (2001), and Swift (1991). By comparing the results of different nasal models built from MRI scans of the same individual, but with different

manufacturing methods (summarized in Section 2.3.1), it can be seen that that deposition is larger when surface roughness is larger. Garcia et al. (2004) investigated the effect of nasal cavity geometry on particle deposition fraction. Their results showed that for the same impaction parameter, the wider nasal passages (subject 1 and subject 3, male) had higher particle deposition efficiencies (see Figure 2.6), which indicated that nasal deposition increases as the characteristic diameter of the nasal passages increases..

Figure 2.6 Summary of *in vitro* measurements of nasal deposition fraction

To better understand the patterns of particle deposition, Häußermann et al. (2002) measured the differences in total deposition in the nose arising from differences in the

breathing patterns. The cyclic human breathing patterns in their study were produced by the breathing simulator (Häußermann et al., 2002) based on the data of breathing patterns of a healthy Caucasian male volunteer. Monodisperse particles (diameters varied from 1.7 to 10 μm) were studied in a cast of nasal cavity using different human breathing patterns (maximum flow rates = 10, 20, 30, 40 and 50 L/min) as well as under constant flow rate conditions.

Their results for small particles (between 1.7 and 3 μm) showed a much higher deposition using constant flow rates than deposition caused by cyclic human breathing with the same average flow rate. This difference decreased for higher values of the impaction parameter (i.e., when the particles became larger or flow rate increased). It was conjectured by the authors that the reason could be the different flow conditions in the nasal cavity model caused by different breathing patterns, since it is more likely for cyclic breathing patterns to cause vortices at different locations in nasal cavity than constant flow.

However, it should be noted that Häußermann et al. (2002) acknowledged that their results showed the opposite trend compared with the results of similar particle deposition experiments performed by other researchers using lung cast (Gurman et al., 1984). In addition, steady flow might be more realistic than cyclic flow in the drug delivery. In present numerical and experimental investigation of particle deposition in the standardized human nasal cavity, the target application is medical drug delivery. Thus, steady flow rates were used instead of cyclic flow.

2.4 Numerical simulation

Numerical simulation using computational fluid dynamics (CFD) is also a very useful, and widely adopted tool for studying nasal aerosol deposition, which is in general much easier to implement than experiments. However, CFD has its own disadvantages and limitations, one of these limitations being the reliability of the obtained results. The reliability of results is dependent on factors such as the numerical algorithms of the equations, the mathematical formulation used to process the simulation, the boundary conditions, etc. Furthermore, where turbulent flow is concerned, the chosen turbulence model is important; it is difficult to choose because there is no single turbulence model that can reliably predict all turbulent flow with sufficient accuracy.

2.4.1 Overview of simulation of particles in turbulent flow

To model numerically the particle-fluid two-phase flow, it is important to clarify the coupling between the particle motion and its surrounding fluid and thus determine the appropriate numerical method. Elgobashi (1994) presented an overview of the simulation of particles in turbulent flows and proposed a map of interactions between particles and fluid turbulence. This map of interactions is shown in Figure 2.7.

Figure 2.7 Interactions between particles and fluid turbulence

The quantities in the dimensionless coordinates shown in Figure 2.7 are defined below.

Φ_p : volume fraction of particles, $\Phi_p = MV_p / V$

M : number of particles

V_p : volume of a single particle

V : volume occupied by particles and fluid

d : diameter of particle

τ_p : particle response time, $\tau_p = \rho_p d^2 / (18\rho_f \nu)$ for Stokes flow

τ_K : Kolmogorov time scale, $\tau_K = (\nu / \varepsilon)^{1/2}$

τ_e : turn-over time of a large eddy, $\tau_e = l / u$

ν : kinematic viscosity of the fluid

- ρ : material density and the subscripts p and f denote respectively the particle and carrier fluid
- l : length scale of the energy containing eddies,
- u : RMS fluid velocity
- ε : the dissipation rate of turbulence kinetic energy.

For very low values of dispersed-phase volume fraction ($\Phi_p < 10^{-6}$), the particles have negligible effects on turbulence, and the interaction between the particles and turbulence referred to as “one-way coupling”. This means that in this regime, particle dispersion, depends on the state of turbulence, but due to the negligible concentration of the particles, the momentum transfer from the particles to the turbulent flow has an insignificant effect on the flow. In the second regime, $10^{-6} < \Phi_p < 10^{-3}$, the momentum transfer from the particles is large enough to alter the structure of the turbulence. This interaction is called “two-way coupling”. In this regime, and for a given value of Φ_p , lowering the ratio of the particle response time τ_p (e.g. smaller particle diameter for the same particle material and fluid viscosity) increases the surface area of the particulate phase, hence increasing the dissipation rate of turbulence energy. Moreover, as τ_p increases for the same Φ_p , the particle Reynolds number, Re_p , increases and at values of $Re_p \geq 400$, vortex shedding takes place resulting in enhanced production of turbulence energy. This means that the existence of particles can augment the turbulence if the ratio of the particle response time to the turnover time of a large eddy is greater than unity, or can attenuate turbulence if the ratio is less than unity. The vertical coordinate (τ_p/τ_e) is related to the other coordinate (τ_p/τ_k) by the turbulence Reynolds number ($Re_\lambda = ul/\nu$)

since $(\tau_p/\tau) = \text{Re}_\lambda^{1/2}$. Flows in the first two regimes discussed above are often referred to as dilute cases. In the third regime, $\Phi_p > 10^{-3}$, flows are referred to as dense cases. Here, in addition to two-way coupling between particles and turbulence, particle/particle collisions take place, and this regime is called four-way coupling. As Φ_p increases and approaches 1, a granular flow in which there is no fluid is obtained.. The current research is concerned with dilute flows only in which one-way coupling can be assumed.

Interactions between turbulence and particles involve: 1) turbulent dispersion of the particles (the effects of turbulence on the particles), and 2) modification of the carrier-phase turbulence structure (the effects of the presence of particles on the turbulence). Since one-way coupling will be assumed in present work, only turbulent dispersion of the particles will be taken into account in the present simulation. Particle dispersion in turbulence is often simulated using the stochastic (Monte Carlo) method, in which the turbulent field is represented by a random number generator. Conventional stochastic Lagrangian computations are also called stochastic discrete-delta function models (Chen and Pereira, 1998).

2.4.2 Modeling methodology

Prediction of particle deposition is usually handled in one of two approaches (Mashayek and Pandya, 2003). The first approach is Eulerian, where particles are assumed to move toward the adjacent wall by turbulent diffusion and then reach the wall by a free flight mechanism (see Friedlander and Johnstone, 1951; Ganic and Mastanaiah, 1981; Jackson et al., 1997). The second approach is Lagrangian, which is also called “trajectory model”

where trajectories of individual particles are calculated by solving the particle equation of motion. In the most commonly used Lagrangian approach, the single-phase flow is calculated by using RANS (Reynolds averaged Navier–Stokes) equations (for example, the $k-\varepsilon$, $k-\omega$, and shear stress transport, SST, turbulence model equations), LES (large eddy simulation), or DNS (direct numerical simulation), then individual particles are numerically released in the computational domain by following the particle equation of motion. The Lagrangian approach has a computational expense that is higher than the Eulerian approach (Elgobashi 1994), but it is able to provide a more realistic and flexible model of particle deposition than the Eulerian one. As noted above, when the particle concentration is very low, the primary flow is assumed to be unmodified by the presence of particles (i.e., “one-way coupling”); this assumption significantly facilitates simulations of particle motion. On the other hand, when the particle concentration is not very low, the mutual interaction between the primary flow and the particles must be incorporated into the simulation (i.e., “two-way coupling”).

The most sophisticated and accurate approach for modeling particle deposition in turbulent boundary layers is DNS. In DNS the Navier-Stokes equations are solved without modeling and the main characteristics of the flows can be correctly predicted by DNS. DNS has been used successfully in a number of studies that have increased our fundamental understanding of many of the mechanisms governing deposition (McLaughlin, 1989; Brooke et al., 1994). However, DNS is extremely expensive and requires large computational time, as the grid density required is proportional to Re^3 (Luo et al., 2004). Thus, for high Reynolds numbers and complicated geometries, such as human airway geometry, the mesh sizes required for DNS are prohibitive.

LES is an approach which is not as severely restricted in the range of Reynolds numbers as DNS. In LES, the large, energy-containing scales of motion are calculated directly, while only the effect of the smallest (subgrid) scales of motion are modeled. This approach works well since particle dispersion is determined mainly by the large scales. Thus, LES is being used increasingly in calculations of turbulent flows (Akselvoll and Moin, 1993; Squires and Piomelli, 1995) and prediction of particle deposition in turbulent flows (Wang and Squires, 1996; Yuu et al., 2001; Pandya and Mashayek, 2002).

The Eddy-particle interaction model is a Lagrangian approach used to track particles in the simulation of flows laden with particles. Given initial conditions of velocity and position, the motion of a single particle is calculated by treating it as a series of interactions with discrete eddies having a characteristic size (eddy length), lifetime and velocity. Graham and James (1996) classified eddy interaction models, which have appeared in the literature, into the following three types:

(1) The characteristic eddy scales remain constant throughout the flow (Hutchinson *et al.*, 1971; James *et al.*, 1980);

(2) The characteristic eddy scales are obtained from a numerical simulation of the turbulent primary flow (Gosman and Ioannides, 1981; Govan *et al.*, 1989; Kallio and Reeks, 1989);

(3) Alternative models, in which, besides representative length scale, lifetime and velocity scale, other forms of Lagrangian or Eulerian velocity auto-correlation functions were required (Berlemont *et al.*, 1990; Burry and Bergeles, 1990)

From a practical point of view, the use of the Reynolds-averaged Navier-Stokes (RANS) equations, such as the $k-\varepsilon$ and $k-\omega$ turbulence model equations, is a cost-effective and preferable way to predict the primary flow. Though the RANS equations provide only one-point turbulence statistics, it is of great significance to demonstrate that once correct turbulence statistics are given, the one-way coupling Lagrangian Eddy-particle interaction model (EIM) can give adequate prediction of particle deposition on the walls. It is foreseen that a combined use of RANS/EIM equations with newly emerging experimental techniques will provide a way of predicting accurate near-wall turbulence statistics of the primary flow and particle deposition in the nasal cavity through careful optimization of parameters in the RANS equations.

Both DNS and LES require no model for the calculation of the particle trajectories, since they provide the filtered and the actual instantaneous values of fluid velocities, but they are computationally much more expensive than the RANS/EIM approach. Both experimental (aerosol deposition) and numerical methods (RANS/EIM, LES) will be explored in the present work to simulate the airflow and deposition patterns in a realistic and idealized nasal cavity.

2.4.3 Previous Simulations of particles in human respiratory tract

CFD simulations can be used in the prediction of detailed total and regional deposition patterns within the human respiratory tract, which are currently difficult to determine from *in vivo* or *in vitro* experiments. Much work has been done to investigate particle deposition in the human respiratory tract using CFD, e.g., DeHaan (2001) and Matida et al. (2003) in the oropharynx (mouth-throat), Zhang et al. (2003) using oral airways (i.e.,

mouth to trachea), Tang et al. (2004), Inthavong et al. (2006), Liu et al. (2007), Tian et al. (2007), Shi et al. (2007), and Shanley et al. (2008) using the nasal tract (summarized in Table 2.3), Yu et al. (1998) for particle diffusion in human upper respiratory system and Sarangapani and Wexler (2000) using an extrathoracic model (i.e., nasal to larynx).

Table 2.3 Summary of previous numerical simulations of particle deposition in human nasal cavity

Researcher and year	Data source of geometry of nasal cavity	Simulation environment and method	Flow rates, particle sizes and density	Other information
Inthavong et al., 2006	CT scans of a 25-year-old healthy, non-smoking Asian male (73 kg, 173 cm)	FLUENT6.1.2; realizable k- ϵ model for airflow simulation, hybrid Lagrangian particle tracking method (Discrete Random Walk model and mean flow tracking)	20, 30 and 40 L/min; 1~30 μm ; 1000 Kg/m ³	Smooth wall; particles deposit when touch the wall
Liu et al., 2007	CT scans of a healthy 25-year-old man (Kelly et al, 2000); improve the nostril	CFX 5.1; SST (Shear Stress Transport) k- ω based Model and LES for airflow simulation; Eddy Interaction Model (turbulent tracking and mean flow tracking)	7.5,15,30,45 and 60 L/min; 0.35~16 μm ; 913 Kg/m ³	Smooth wall; particles deposit when touch the wall
Tian et al., 2007	The same as Inthavong et al., 2006.	FLUENT6.1.2; Laminar flow; Lagrangian particle tracking method	10 L/min; 3, 6.2, 9.1, 11.9,16, 20, 25, 30, 39.2, 48.3, and 55 μm , 560, 590; 930 Kg/m ³	Smooth wall
Shi et al., 2007	MRI scans of a 53-year-old non-smoking Caucasian male	CFX 10; Laminar flow; Lagrangian particle tracking algorithm	7.5 and 20 L/min; 1~50 μm ; 1000 Kg/m ³	Smooth wall and wall with a 0.2mm wall roughness layer
Shanley et al., 2008	MRI scans of an anonymous, healthy, adult male human subject	FLUENT; Laminar flow; Lagrangian particle tracking algorithm; discrete-phase model (DPM) within FLUENT	2, 3, 4, 5, 6, and 7 L/min; 1~10 μm ; 1000, 2000, and 3000 Kg/m ³	Smooth wall; particles deposit when touch the wall

Figure 2.8 shows results of previous deposition simulations of several other researchers (Inthavong et al., 2006; Tian et al., 2007; Shi et al., 2007; Shanley et al., 2008). Although the nasal cavity models of cited works were generated from different subjects (Inthavong et al., 2006 and Tian et al., 2007: CT scans of a 25-year-old healthy, non-smoking Asian male; Shi et al., 2007: MRI scans of a 53-year-old non-smoking Caucasian male originating from Swift (1991); Shanley et al., 2008: MRI scans of an

anonymous, healthy, adult male human subject), these results show similar trends. While for larger impaction parameters ($d_a^2 Q > 1000$), differences in the values of deposition fraction at fixed values of the impaction parameter are not insignificant (especially for the simulations of Shanley et al., 2008 and Tian et al., 2007), indicating the importance of inter-subject variability.

For larger impaction parameters ($d_a^2 Q > 1000$), the numerical simulations results show under-prediction to some extent when compared with previous in vitro deposition data (see Figure 2.8). This difference is likely attributable to an effect of wall roughness. In the numerical simulation, the boundary condition for the wall of nasal cavity was specified as smooth, whereas there is a small but unavoidable wall roughness along the inner wall of the in vitro model due to manufacturing (see Kelly et al., 2004). Shi et al. (2007) also took the wall roughness into account using a 0.2 mm wall roughness layer, and the simulated results showed that this wall roughness height could enhance the particle deposition.

Figure 2.8 Previous simulation results of particle deposition fraction

2.5 Geometry Related Limitations of Previous Work

As discussed above, many efforts have been made to measure characteristics dimensions of human nasal cavity and to create 3D human nasal cavity models, and many experimental (*in vivo* and *in vitro*) and numerical studies have been conducted on particle deposition in the human nasal passages. Although these studies have shown that deposition fraction is mainly a function of particle size and density, airflow rate and nasal airway geometry, these studies are somewhat limited and difficult to compare since they were all completed using geometries of individual human subjects. To the author's knowledge, no previous investigations have been performed in a standardized human

nasal geometry representing the general population in the context of aerosol medication deposition. Moreover, detailed numerical and experimental investigation of regional particle deposition, which is a significant issue in terms of improving nasal drug delivery techniques, has not been shown in previous studies.

Chapter 3: Construction of realistic models of the human nasal cavity

The material presented in this chapter has been published in a refereed journal article co-authored by the author of this thesis, her supervisors, and two collaborators at the Ottawa Civic Hospital as: Y. Liu, M.R. Johnson, E.A. Matida, S. Kherani, J. Marsan (2009) Creation of a Standardized Geometry of the Human Nasal Cavity, Journal of Applied Physiology, 106: 784-795, 2009. While the text was written jointly, the CT scan measurements and image processing of individual scans and models were performed by the author.

A model that realistically represents the human nasal cavity is indispensable for studying, both numerically and experimentally, the airflow and particle deposition patterns in the human nasal cavity. Although several investigations reviewed in Chapter 2 have been performed to measure basic characteristic dimensions of the human nasal cavity using acoustic rhinometry (AR) (Hilberg et al., 1989; Min and Jang., 1995; Cheng, K. H. et al., 1996; Corey et al., 1997; Kesavanathan and Swift, 1998; Terheyden et al. 2000), magnetic resonance imaging (MRI) (Cheng, Y. S. et al., 1996; Cheng, K. H. et al., 1996; Corey et al., 1997; Guilmette et al., 1997), computed tomography (CT) (Min and Jang, 1995; Terheyden et al. 2000), and using an *in vivo* cast (Swift and Kesavanatha.,1996), no previous researchers have published a median human nasal geometry that can be used to study airflow patterns and aerosol deposition patterns. Thus, the creation of a standardized three-dimensional human nasal cavity geometry which can represent the general population, as well as the establishment of a procedure for developing geometries of specific population subsets, would be an important and significant development that could benefit the research of nasal drug delivery as well as many other fields, such as nasal surgery, nasal toxicology, risk assessment, and disease diagnosis.

3.1 Baseline Data Used to Create a Standardized Human Nasal Cavity Model

Research to develop a standardized human nasal cavity model was completed in cooperation with the department of Otolaryngology at the Ottawa Hospital, Civic campus, which provided coronal CT scans for thirty healthy adult subjects whose nasal cavities were considered as normal and without any anatomic abnormalities. In keeping with the hospital's code of ethics all subjects, from whom the CT scans were obtained, remained anonymous throughout the entire study.

All scans were reviewed carefully and confirmed by a doctor of the department of Otolaryngology at the Ottawa Civic Hospital to have nasal anatomy considered to be within normal limits. Specifically, there were no obstructing lesions and the septum was not deviated. When the CT scans were taken, all subjects were in normal condition and decongested.

The age and gender of each subject were recorded as well as the characteristics of CT scans; this information is summarized in Table 3.1. The age of subjects ranged from 17 to 78 years (median of 45); there were 13 males and 17 females. Ethnicity was not specifically tracked as part of the original examinations and thus these data were not available. However, the included scans were chosen randomly and indiscriminately to include all available normal scans of patients presenting at the department of Otolaryngology. Thus, even though there was no explicit information regarding the ethnicity of the subjects, the ethnic backgrounds could be expected to comprise an

unbiased sample of the Ottawa, Ontario, Canada population (predominantly Caucasian with 16% visible minorities including 4.0% Black, 2.9% Chinese, and 2.5% Arab as reported by Statistics Canada, 2008). The distance between consecutive slices was 2.5 mm, except in 3 subjects for which cuts were 1 or 2 mm apart. The resolution of CT scans varied from 0.24 to 0.348 in mm/pixel.

Table 3.1 Information about the subjects and CT scan of 30 individuals in current study

Subject No.	Gender	Age	Number of scan planes	Distance between slices (mm)	Resolution in x-y plane (mm/pixel)
1	F	45	38	2.5	0.325
2	M	59	40	2.5	0.325
3	F	63	39	2.0	0.24
4	F	36	38	2.5	0.325
5	F	20	40	2.5	0.325
6	F	49	36	2.0	0.325
7	F	30	32	2.5	0.325
8	M	74	43	2.5	0.325
9	M	60	42	2.5	0.325
10	F	17	39	2.5	0.325
11	M	56	40	2.5	0.325
12	M	52	44	2.5	0.325
13	M	39	40	2.5	0.325
14	F	37	38	2.5	0.325
15	M	52	43	2.5	0.3
16	M	41	39	2.5	0.293
17	F	78	43	2.5	0.339
18	F	26	41	2.5	0.245
19	M	52	42	2.5	0.283
20	F	23	44	2.5	0.313
21	M	52	39	2.5	0.325
22	F	45	34	2.5	0.325
23	F	52	38	2.5	0.325
24	F	30	45	2.5	0.325
25	F	34	41	2.5	0.325
26	F	66	80	1.0	0.348
27	F	49	42	2.5	0.325
28	M	36	40	2.5	0.325
29	M	42	47	2.5	0.293
30	M	45	40	2.5	0.293
AVERAGE		45.3	41.57	2.417	0.315
MEDIAN		45	40	2.5	0.325
MAX		78	80	2.5	0.348
MIN		17	32	1	0.24

3.2 Generation and alignment of individual 3D nasal cavity models

3.2.1 Construction of coarse 3D models from CT scans

To construct models from CT scans, first, all sets of raw 2D CT images were processed using 3D-DOCTOR (Able Software Corp., Lexington, MA, USA) to produce coarse, 3D nasal cavity geometries (including both left and right nasal airways) for each of the subjects. The procedure is illustrated in Figure 3.1 and is described below:

- (a) Images were imported and calibration parameters were set (i.e. image resolution and distance in between scans), as shown in Figure 3.1a. Three spatial coordinates, x, y, z, were used in the 3D-DOCTOR software. The correct setting of image resolution ensured the real size of each CT scan, and the distance in between scans was used to get the correct length along z direction.
- (b) Images were segmented (using the texture-based auto-segmentation function within 3D-DOCTOR software) and boundaries were processed, as shown in Figure 3.1.b. In present work, the paranasal sinuses (the air-filled pockets located within the bones of the skull surrounding the nasal cavity) were excluded from the nasal model. The segmenting parameter of 3D-DOCTOR software was adjusted to make the boundaries of the paranasal sinuses distinct from those of the main nasal passageway.
- (c) Surfaces were rendered and coarse 3D models were exported (as shown in Figure 3.1.c).

a

b

c

Figure 3.1 Procedure of generation of coarse nasal cavity model using 3D-Doctor software

In present study, the main nasal passage is the only domain we are interested in. Thus, the paranasal sinuses are excluded. During processing of the raw CT scans, the paranasal sinuses were easily distinguished from the main nasal passageway and excluded by adjusting the segmenting parameter within the 3D-DOCTOR software.

3.2.2 Rotational alignment of coarse 3D models

In general, CT scans are taken in three basic orientations: coronal, transverse (also called axial) or sagittal. In the present study, the CT scans offered by the hospital are all in the coronal plane. There is no precise method of positioning subjects or defining a measurement origin, thus the 3D orientation of each set of CT scans varies. It can be noticed from Figure 3.2 that there is an apparent rotational misalignment toward the clockwise direction of the sample raw CT images.

Before direct comparisons or physical measurements can be made, all of the generated coarse 3D models needed to be rotated and aligned to a commonly defined position. Sufficient geometric constraints were applied to satisfy six degrees of freedom (e.g., three spatial coordinates, x , y , z of a common origin and three independent rotation angles about this origin). A multistep procedure was developed for providing the necessary geometric constraints and will be explained in detail in the following sections.

3.2.2.1 Specifying the landmark and choana from the raw CT scans

First, a common “landmark” on each set of CT scans was determined. The tip of the anterior maxillary spine, or the point where the nasal septum intersects the maxilla bone, was chosen as the first landmark (Figure 3.2.a). This location was identifiable on each set of coronal plane CT scans and was representative of the anterior region of the nose. The mean length of the anterior maxillary spine of all 30 subjects was determined to be 6.5 ± 1.9 mm. Thus, the uncertainty in defining this location was smaller than the spacing between CT scans. The landmark was identified on each model and assigned an arbitrary x-y-z coordinate location of (0 mm, 0 mm, 0mm), thus removing three degrees of freedom. A second constraint was developed by identifying the point on a posterior coronal plane where the two nasal airways merge, known as the choana or the opening into the nasopharynx (Figure 3.2.b). The imaginary line joining the anterior maxillary spine and the choana was then used to define the nominal plane of symmetry.

Figure 3.2 Identification of the (a) maxillary spine landmark and (b) choana in the raw, coronal plane CT scans

3.2.2.2 Rotating coarse nasal models

The procedure for rotational alignment is illustrated schematically using model No.8 as example in Figure 3.3, which shows the initial (x-y-z) and final, aligned (X-Y-Z) coordinate axes of the coarse nasal model.

The first step of rotational alignment was to rotate the 3D model about the line joining the anterior maxillary spine and the choana until the projected area viewed from the top of the model was minimized, and the x-y plane of symmetry could be fully specified for each model, thus removing two further degrees of freedom. This initial rotation about the imaginary reference line linking the maxillary spine landmark and the choana is indicated by the angle, α , as shown in Figure 3.3. The secondary rotation about the y-axis is given by angle, β . After the first two rotations, the symmetry plane was aligned with the final X-Y coordinate plane.

Figure 3.3 Coordinate system for rotating the coarse 3D nasal cavity model.
Example images show coarse model 8

The procedure for the first two rotations is shown in Figure 3.4.a, b, and c, which shows rendered images of nasal model No. 8 before and after the first two rotations. As previously mentioned, all subjects in the current study were aligned approximately to obtain CT scans in the coronal plane. Thus, the magnitudes of the rotational transformations α and β were small. In the current data, the maximum rotational corrections, α in the coronal (y-z) plane, and β in the transverse (x-z) plane, relative to the orientation of the raw CT scans were all between -5.0° and 4.0° and -2.0° and 5.0° respectively. Even though the magnitude of α and β were small, the first two steps of the rotation were indispensable due to the small size and complexity of the human nasal cavity.

Figure 3.4 Illustration of the first two steps of rotational alignment of a coarse 3D nasal cavity model. (Example images show coarse model 8.) (a) Top view of model before rotation; (b)Top view of model after rotation around imaginary reference line linking the maxillary spine landmark and the posterior merge point; (c)Top view of model after rotation around Y-axis to align symmetry plane with X-axis

The final step of rotational alignment was rotating the model about an axis perpendicular to the plane of symmetry (Z-axis) until the projected area on y-z plane as viewed from the front of the model was minimized. This rotation is indicated by the angle, θ , in Figure 3.4, and an example is shown in Figure 3.5 for model No. 8. θ depends on the rotational pitch of each subject's head during the CT scans, and varied more significantly than α and β among subjects. For the current data, the maximum value of θ was 35.5 degrees.

Figure 3.5 Example images of model number 8 showing rotational alignment of a coarse 3D nasal cavity model. Original orientation is shown in green and final, aligned model is shown in red. The positions of the imaginary reference lines before and after alignment are indicated

All 3D coarse nasal models were aligned using this procedure. With the six degrees of freedom appropriately constrained, the location of the common maxillary spine landmark of each subject was specified, and the direction of the X-Y-Z axes was fixed relative to the nominal plane of symmetry.

3.3 Creation of the standardized human nasal cavity model

3.3.1 *Measuring characteristic length and scaling individual coarse models*

In order to determine a median shape of a standardized 3D nasal cavity, it was necessary to compensate for size variations among subjects, which is difficult because of the high complexity and diversity of the nasal cavity. Before attempting to determine the median geometry of the standardized human nasal cavity model, all coarse aligned nasal cavity models were divided into three sub-regions: the anterior/nostril region (including the part from anterior tip of the nostril to the anterior maxillary spine), the middle/nasal airway region (from the maxillary spine to the choana), and the posterior region (corresponding to the region posterior to the choana known as the nasopharynx), as indicated in Figure 3.6.

Figure 3.6 Three sub-regions of a 3D nasal cavity

For each subject, a characteristic length of the middle/airway region was determined. The characteristic length was defined as the dimension in the X-direction between the anterior maxillary spine landmark to the choana or posterior merge point of the nasal

airways. As listed in Table 3.2, the measured characteristic lengths ranged from 50 mm to 80.5 mm, which reflects gender differences as well as normal variability among subjects. Relative to the average length of 65.1 mm, the standard deviation was 7.2 mm or 11%.

Table 3.2 Measurements of geometric parameters of the middle region of aligned scaled coarse nasal models

Subject No.	Gender	Characteristic length of middle region in X-direction (mm)	Internal volume of middle region of single nasal passage, (mm ³)		Cross-sectional area in middle region of a single passage, (mm ²)	
			Left	Right	Max.	Min.
1	F	60.1	10418	10509	240	111
2	M	67.6	10212	11245	209	68
3	F	50	8745	7523	215	118
4	F	56.7	8934	10000	307	69
5	F	69.3	6468.2	8075	179	52
6	F	60.8	10462	6782	221	52
7	F	62.9	6846	7660	157	67
8	M	66.3	10862	9756	275	68
9	M	65.1	10481	11880	244	67
10	F	67.9	9315	8988	224	71
11	M	64.6	10980	12561	238	103
12	M	73.4	11227	11827	242	85
13	M	60.1	16145	13819	354	82
14	F	60.8	9971	9486	230	82
15	M	57.7	8655	13601	274	82
16	M	61	7066	8111	202	60
17	F	65	10527	9331	213	91
18	F	60	7567	9104	254	50
19	M	78.3	15549	14289	280	78
20	F	65.3	12099	14356	296	97
21	M	72.3	12807	16192	312	89
22	F	65.6	8093	7199	189	59
23	F	63.8	8346	9774	194	58
24	F	77.4	11293	9285	230	43
25	F	61.2	11843	12411	260	102
26	F	53	10747	10751	322	83
27	F	66.3	9127	10432	236	68
28	M	63.6	9951	16435	306	89
29	M	80.5	15989	11660	261	66
30	M	76.6	12283	11002	223	66
	AVERAGE	65.1	10434	10801	246	76
	MEDIAN	64.8	10440	10471	239	70
	STD. DEV.	7.2	2458	2568	46	19
	MAX	80.5	16145	16435	354	118
	MIN	50	6468	6782	157	43

To compensate for size variations and to facilitate computation of a median 3D shape, each of the nasal cavity models was geometrically scaled using the ratio of the averaged characteristic length of all nasal geometries to the characteristic length of that specific geometry:

$$S_i = \bar{L}_M / L_{M,i} \quad (3.1)$$

where S_i is the geometric scale factor for the i th model, $\bar{L}_M = 65.1$ mm and is the averaged characteristic length, and $L_{M,i}$ is the characteristic length of the i th model. Table 3.2 lists geometric parameters of the middle region of aligned scaled coarse nasal models. Most of the scale factors were within 11% and all were within 24% of unity, which clearly shows that the scaling process was generally a small adjustment.

3.3.2 Slicing and smoothing individual coarse models

In addition to the process of aligning and scaling the models, each of the aligned and scaled coarse 3D models was sliced by Y-Z planes along the X-direction using ICEM software (Ansys Inc., Canonsburg, PA, USA) to generate up to 56 coronal plane images spaced 2 mm apart for each of the 30 full nasal models.

As noted previously, the right and left nasal passages of each of the 30 full nasal models in the present study were considered as distinct geometries, thereby increasing the number of subjects. Thus, in the frontal and middle regions of the model (anterior to the choana), each of the coronal plane images generated from the aligned and scaled models was separated into two distinct images containing the boundaries of either the left or right

nasal passages. The images of the left nasal passages were mirrored about the plane of symmetry (determined using the procedure described above), to produce thirty additional sets of images of right nasal airways. This procedure effectively doubled the available sample size to produce a total sample of 60 sets of right nasal airway coronal plane images.

Figure 3.7 shows a plot of the number of coronal plane images available at each X-location along the length of the nasal cavity. The vertical lines on the graph indicate the relative X-locations of the entry into the final nasal model (explained below), the anterior maxillary spine, the choana, and the posterior termination of the final model (within the nasopharynx near the pharyngeal wall). Throughout most of the length of the nasal cavity, 60 cross-sectional (coronal) images were available, which included the region of highest geometric variability.

Figure 3.7 Number of available coronal-plane images at each X-location along nasal cavity

Figure 3.7 illustrates that not all sets of available CT scans extended fully to the tip of the nose and in general they terminated at different locations posterior to the choana. Thus fewer than 60 coronal plane images were available toward the anterior and posterior ends of the model, which means information about the nostril of several nasal cavity models is missing. The solution to this problem will be discussed in following section.

Following the slicing procedure, the boundaries obtained from the 56 cross-sectional images of each coarse model were checked and smoothed using the ICEM software to eliminate any obvious errors generated from 3D-DOCTOR, such as discontinuous curves and/or abnormally sharp or angled edges. The smoothing procedure consisted of four steps as illustrated in Figure 3.8.

Figure 3.8 Example of cross-sectional boundary smoothing. The dashed grey curve is the original boundary, points are manually selected on this boundary, and the black continuous curve is the corrected and smoothed boundary

- (ii) 60~100 points along each boundary curve were selected. (The number of points varied for different lengths of boundary curves);
- (iii) Smoothed boundary curves were created (see Figure 3.8) from these points using the automatic curve-generating function within ICEM, which uses the standard B-Spline algorithm (De Boor, 1978);
- (iv) A set of 56 new, smoothed cross-sectional (coronal) images for each coarse model were exported;
- (v) The smoothed 3D surfaces from the adjusted coronal images of each single passage were rendered using the surface-generating function within ICEM.

Figure 3.9 shows 32 samples of the 60 final coronal plane images at the location 30mm posterior to the maxillary spine landmark in the nasal cavity. In these images, the geometry of the maxillary spine landmark region is the most dramatic of any location along the nasal cavity. Even though all the coronal images have many common characteristics, turbinates for example, their exact shape varies dramatically, again indicating the diversity of these subjects.

Figure 3.9 32 out of 60 nasal cavity cross-sectional shapes located 30 mm from the maxillary spine landmark

3.3.3 Measurement of characteristic dimensions of individual coarse 3D nasal cavity models

As shown in Table 3.2, apart from characteristic length, several measurements (e.g. the internal volume and flow cross-sectional area of single nasal passage) were taken for each aligned scaled smoothed coarse model. The internal volume of the middle section of each single nasal airway was obtained by summing the products of the cross-sectional areas of the coronal planes (that fell in the middle region of the model) and the distance between each of the planes (2 mm). The internal volumes of each single nasal airway

(i.e. left or right airway in the middle region) and the minimum and maximum flow cross-sectional areas in each airway showed significant variability among subjects. The maximum and minimum values of cross-sectional areas for extreme subjects were as much as 55% larger or 43% smaller than average values, which demonstrated the high diversity of the nasal model again.

Table 3.3 Measurements of frontal/nostril regions from 7 sets of CT scans

Subject No.	Gender	Length of frontal region in X-direction (cm)	Length along major axis of nostril at inlet plane (cm)	Width along minor axis of nostril at inlet plane (cm)	Nostril Angle (degrees)	Internal volume of single nasal passage (nostril to choana) (mm ³)		Surface area of single nasal passage (nostril to choana) (cm ²)	
						left	right	left	right
7	F	3.56	2.35	0.92	65.22	10.1	10.8	85.1	85.0
8	M	3.49	2.25	0.65	68.94	15.3	12.0	113.5	110.9
9	M	3.24	2.64	0.74	70.08	13.6	15.3	107.9	101.1
11	M	3.42	2.10	0.87	69.76	14.8	16.3	102.2	104.2
15	M	4.29	2.15	0.97	67.71	10.8	14.6	115.1	107.6
23	F	3.05	1.83	0.56	68.55	11.3	12.4	79.7	85.4
27	F	3.19	2.06	0.83	68.23	13.2	14.1	109.8	112.3
AVERAGE		3.46	2.2	0.79	68.36	13.18		101.4	
STD.DEV.		0.41	0.25	0.15	1.61	1.97		12.28	
MAX		4.29	2.64	0.97	70.08	16.25		79.74	
MIN		3.05	1.83	0.56	65.22	10.13		115.05	

As stated previously, not all of the available sets of scans had information extending to the anterior tip of the nostrils. Table 3.3 summarizes measured dimensions for the anterior/nostril region of the nasal models using the available seven complete sets of scans which represent 14 single nasal passageways. The total volume and surface area of seven complete nasal cavities can be seen in Table 3.3. Similar to the internal volume measurement, the surface area of each nasal cavity was obtained by summing the product of the perimeter (i.e., the length of the outline of the image) and the inter-plane distance

(i.e., 2 mm) for each coronal plane. This was done for the entire length of the nasal cavity. As shown in Table 3.3, there is variability in the length and width of the nostrils as well as the angle between the major axes of the nostril in the entry plane, which is consistent with previous studies results by Kesavanathan and Swift (1998).

3.3.4 Image processing methodology for generating median coronal plane images

Because of the significant variability throughout the individual nasal cavities, a novel and sophisticated image processing protocol was created and adopted here to fulfill the goal of generating a meaningful standardized cavity model.

For each of the 56 X-locations, the coronal cross-sectional images were processed to produce a median cross-sectional shape at that location. Several in-house algorithms were developed to aid this process using image-processing tools from Labview (National Instruments Corporation, Austin, TX). Using physical shape and area as constraints, these algorithms allowed statistically based estimation of median cross-sectional geometries through a procedure of ensemble averaging, thresholding, and edge detection. Figure 3.10 a-d shows various stages of the image processing using images for a coronal plane at 30 mm X-location relative to the maxillary spine landmark as example. This region of the nasal cavity exhibited the maximum geometric variability and presented the greatest challenge in determining a median shape. The full analysis procedure involved four steps as described below and shown in Figure 3.10.

Figure 3.10 Example coronal plane images at X=30 mm obtained during processing to determine the characteristic cross-sectional geometry. a) ensemble averaged grayscale image; b) binarized 50% threshold (“median”) image; c) median image in red overlaid on top of “median area” image in yellow; d) final boundaries of cavity at current X-position in yellow, at next upstream position in green, at next downstream position in red, overlaid on median image in blue

(i) All cross-sectional images at each X-location were classified as one group, and then were binarized (intensities of pixels located within the boundary were set to unity while pixels outside the boundary were set to zero) and summed (intensities at corresponding locations in all of the images were added up pixel by pixel). Thus, a single, ensemble averaged grayscale image for each of the 56 X-locations in the model was generated. Figure 3.10.a shows the sample averaged grayscale image for X=30 mm.

(ii) The second step was generating a “median” image. The “median” image is the pixel by pixel collection of all points that fell within at least 50% of the nasal cavities in the ensemble averaged grayscale images created in step (i). To accomplish this goal, a 50% threshold was defined as a threshold value equal to half of the total number of available images, and then was applied to produce a binary image where pixels with value 1 fell within at least 50% of cavities and pixels with value 0 did not. A sample median image

for $X=30$ mm is shown in Figure 3.10.b. The image in Figure 3.10.b is jagged and discontinuous because of the significant geometric variability at this location. This example represents the worst case of the cross-sections; at other locations there was less variability, and the median image was quite smooth.

(iii) Apart from the median image, a separate “median-area” image was also generated at each X location using a different threshold value. This “auto-threshold” value was iteratively chosen so that the cross-sectional area in the median-area image would match the median cross-sectional area calculated from up to 60 available images for that location. As shown in Figure 3.10.c, the “median” image from step (ii) is in red, and is over-laid on the “median-area” image in yellow for $X=30$ mm. It should be noted that the characteristic shape of the nasal airway at this location is much more apparent.

(iv) Using the superimposed images it was possible to make minor manual edits to the shape of the cross-sectional image while constraining the area to match the median cross-sectional area of all available subject images. As shown in Figure 3.10.d, to further aid the final editing process, the canny edge detection algorithm (Canny, 1986) was used to calculate and overlay the contours of the nasal cavity geometry from adjacent cross-sections. As shown in Figure 3.10d, the working contour at $X=30$ mm is shown in yellow while the adjacent upstream contour at $X=28$ mm is shown in green and the adjacent downstream contour at $X=32$ mm is shown in red. These contours are overlaid on the median-area image which is shown in blue. By several iterative edits and adjustments, the final contour shapes at each cross-section are obtained.

The sample images shown in Figure 3.10 are from the most geometrically variable region of the nasal cavity and hence represent the most challenging X -position for

determining a characteristic, median geometry. In general, only very minor edits - if any - were required at most X-locations. All sets of images for each of the 56 X-positions along the nasal cavity were processed using the procedure described previously, and then 56 cross-sectional shapes for the standardized human nasal cavity were obtained, which are shown in Figure 3.11.

Figure 3.11 56 cross-sectional shapes for the standardized human nasal cavity

3.3.5 Determine the shape of nostril and outlet of the standardized nasal cavity

As previously mentioned, at the nostril entry plane, where there were less data available, the averaged physical descriptors (e.g. major and minor axis lengths in the nostril entry plane and angle between the major axes) were calculated from the measured data (shown in Table 3.3) and supplemented with the measured results of Kesavanathan and Swift (1998). Table 3.4 gives the combined averaged physical descriptors (current data merged with data from Kesavanathan and Swift, 1998) at the nostril entry plane, which were used to determine the shape of the inlet plane of the standardized nasal cavity model.

Table 3.4 Averaged dimensions of the nostril inlet plane (merged raw data from Table 3.3 and from Kesavanathan and Swift (1998)) compared with final values for the Carleton-Civic Standardized Model

	Mean±std	Range	Standardized Model
Length of major axis	1.76±0.43 cm	1.18–2.64 cm	1.77
Width of minor axis	0.72±0.12 cm	0.50 cm - 0.97 cm	0.72
Nostril Angle	53.00±16.61°	17.5°–70.1°	67.7°

In the posterior region of the cavity, the two separate airways fuse into a single passageway at the choana, which spans the symmetry plane. Thus, as shown in Figure 3.7, the number of available cross-sectional images suddenly drops from 60 to 30 at the merge point. However, since the goal of this work was to develop a single-sided nasal cavity model, and to remain consistent with the procedure described above, the cross-sectional images past the choana were split and mirrored about the symmetry plane. In the final, standard cavity model detailed below, only half of the airway (patient's right

side) is shown. Thus, if the final model were copied and mirrored, a full two-sided nasal cavity could easily be produced.

3.3.6 Construction of the final Carleton-Civic standardized nasal model

Similar to the generation of coarse models, all of the 56 final cross-sectional images were imported into 3D-DOCTOR software (Able Software Corp., Lexington, MA, USA) to generate a coarse standardized nasal model. This coarse standardized model was imported into ICEM (Ansys Inc., Canonsburg, PA, USA) and was smoothed using the same procedure described in section 3.1.3.4 to create the final, “Carleton-Civic” standardized nasal model. Figure 3.12 shows three views of the final standardized human nasal cavity model.

Figure 3.12 Final standardized nasal cavity model. a) Top view, b) Side view; c) Bottom view

3.4 Analysis of the Carleton-Civic standardized nasal model

Prior to using the standardized nasal model to perform experimental and numerical simulations, it is necessary to analyze the model to make sure it can demonstrate the complex geometric features of the nasal passageway as well as a median size and flow cross-sectional area of human nasal cavity.

Figure 3.13 shows the cross-sectional area (CSA) of the standardized nasal model as a function of the distance from the maxillary spine landmark (which is used here as the reference point), compared with the local, median, and averaged CSAs of all subjects used in this research.

Figure 3.13 Cross-sectional area of the Carleton-Civic standardized nasal model (green curve) compared with individual (dots), median (red curve), and average (blue curve) cross-sectional areas from all available subjects

It can be seen from Figure 3.13 that the values of CSA among the 60 nasal cavities vary significantly, which indicates significant variability throughout the 60 individual nasal cavities. However, the CSA of the new standardized geometry very closely tracks the median value of the CSA from all subject cavities, especially in the complex turbinate region. There is a slight deviation in the anterior nostril region, approximately 2 cm upstream of the maxillary spine; however, the difference is insignificant relative to the notable variability among all models and is negligible when comparing it with the 14 complete nasal cavity models (see Figure 3.14).

Figure 3.14 Cross-sectional areas of the standardized nasal model (green curve) and 14 complete nasal passages (black curve). Running average of the 14 complete curves is shown for comparison in blue

Figure 3.14 shows flow cross-sectional areas of the standardized nasal cavity compared with the data of the available 14 complete nasal passages, which allows a closer examination of the CSAs in the nostril region. Data are plotted as a function of distance relative to the tip of the nostril and without any geometric scaling to permit a more critical comparison.

The minimum CSA (MCA) of the nasal models occurs in a region 20-35 mm from the tip of nostril; the corresponding airway narrowing is called the nasal valve. For the standardized model, the MCA occurs at a location 24 mm from the nostril, which agrees very well with the averaged curves of 14 cavities. The CSA then increases as expected in the region of the turbinates (35-75 mm from the nostril). The data shown in Figure 3.14 indicate that the standardized model effectively captures key geometrical features of the nasal cavity. The axial position of the local maximum in CSA for the standardized model is upstream of the running average local maximum CSA for the 14 complete cavities (dimensionless distance relative to the tip of the nostril equal to 0.12 vs. 0.18). This deviation comes from the fact that the anterior part of the standardized model was generated using available data from all geometries, not just that from the 14 complete nasal cavities.

Figure 3.15 shows the CSA of the standardized nasal model as a function of the distance from the nostril, compared with available CSA data extracted from previous published literature, including CT scan derived data (Min *et al.* (1995), Terheyden *et al.* (2000) and Kelly *et al.* (2000)) and MRI derived data (Cheng Y.S. *et al.* (1996) and Corey *et al.* (1997)).

In Figure 3.15, data are plotted as X-position relative to the tip of the nostril using coordinate data as reported. It is important to note that some alignment bias (such as the position of the head of subjects when the CT scans or the MRI data were obtained) would be expected among data in the literature in the absence of a common and rigorous alignment protocol. Because of the generally elongated shape of the nasal cavity, relative misalignment about the Y or Z axes should lead to higher estimates of CSA.

Figure 3.15 Comparison of cross-sectional areas of the Carleton-Civic standardized nasal model (green curve) with published CT scan derived data from Min and Jang (1995) (orange and red curves), Terheyden *et al.* (2000) (crosses / blue curve) and Kelly *et al.* (2000) (circles); and MRI derived data from Cheng Y.S. *et al.* (1996) (inverted triangles / purple curve) and Corey *et al.* (1997) (yellow curve)

Similar to the data of the present 60 nasal models, there was significant dispersion in the individual geometry data of previous researchers; however, the standardized model agrees very well with all data at the anterior tip of the nasal passage, and there is a generally consistent trend among averaged data of multiple geometries. In particular, the standardized model CSA characteristic correlates well with the averaged data of 4 cavities from Cheng *et al.* (1996) (where the reported CSA for the full two-sided cavities have been halved for comparison) and 12 single-sided cavities from Terheyden *et al.* (2000). On careful observation, the standardized model is on the lower side of the dispersed CSA values in Figure 3.15 . It is not necessarily unexpected and can be explained because the current data is slightly biased toward female subjects (13M/17F) and the cited data from the literature is heavily biased toward male subjects (33M/13F). The data from Min and Jang (1995), which reflect an identical sample size to the current study, do not seem to correlate as well with all of the other data. Although data from Min *et al.* (1995) span a narrower range, an overall flatter trend in CSA with distance is apparent.

Total volume and surface area of our standardized model (from tip of nostril to choana, single passage) were also measured using the same method explained in the section 3.3.3. Total volume of the standardized model was 13.19 cm^3 and total surface area was 90.69 cm^2 . Guilmette *et al.* (1997) measured values between 7.37 and 16.91 for volume (average 8.9 cm^3) and 75.24 and 124.47 (average 91.65 cm^2) for surface area. The surface area of the standardized model agrees with the results of Guilmette *et al.* very well, while the value of total volume is bigger than the averaged value reported by Guilmette *et al.* It is conjectured that the difference is due mainly to the highly complex

nasal geometry and to differences in the definition of the beginning and end of the nasal cavity. Guilmette *et al.* calculated the surface area and volume from the anterior nostril to the posterior end of the nasal airway prior to the nasopharynx.

Based on the above discussion, it can be concluded that the methodology for aligning the coarse nasal models and producing median cross-sectional images has been successfully demonstrated through the production of a standardized nasal geometry. This geometry can be used as a standardized human nasal cavity model because it respects and maintains complex characteristic features of the nasal passageway, while tracking a median size and flow cross-sectional area.

Chapter 4: Methodology of experimental measurement of particle deposition in human nasal cavity

4.1 Construction of physical nasal model

Taking into account the complex flow passage of the human nasal cavity, the rapid prototyping technique was used to construct a physical nasal cavity model for the present particle deposition experiment. The physical nasal model can be constructed using two different methods: one method directly uses the rapid prototyping technique, and the other method uses model casting from the prototype.

4.1.1 *Rapid prototype technique*

Rapid prototyping is the automatic construction of physical objects using solid freeform fabrication. In brief, rapid prototyping takes virtual designs (from computer aided design (CAD) or from animation modeling software), transforms them into cross sections, still virtual, and then creates each cross section in physical space, one after the next until the model is finished.

The first techniques for rapid prototyping became available in the 1980s and were used to produce models and prototype parts. Today, they are used for a much wider range of applications and are even used to manufacture production quality parts in relatively small numbers. Some sculptors use the technology to produce complex shapes for fine art exhibitions.

It offers advantages in many applications, compared to classical subtractive fabrication methods such as milling or turning:

(1) Objects can be formed with any geometric complexity or intricacy without the need for elaborate machine setup or final assembly;

(2) Objects can be created in a relatively short time. Of course, the word "rapid" is relative: construction of a model with contemporary machines typically takes 3 to 72 hours, depending on machine type and model size. Used in micro technologies "rapid" is correct. The products created are ready very quickly, and the machines can build the parts in parallel;

(3) Objects can be made from multiple materials or from composites, or materials can even be varied in a controlled fashion at any location in an object;

(4) Additive fabrication systems reduce the construction of complex objects to a manageable straightforward and relatively fast process;

(5) In essence, these machines are three-dimensional printers with a range of accuracy.

These advantages and properties have resulted in the wide use of this method as a way to reduce time in manufacturing and to create model parts used in laboratory research.

4.1.2 Creation of physical nasal model using RP machine

Full geometric details of the standardized idealized human nasal cavity model, as described in chapter 3, were translated to STL format, which approximates the surfaces

of a solid model with triangles and describes the negative flow passage of the standardized nasal cavity model in the present study. The STL file format has become the Rapid Prototyping industry's standard data transmission format, and almost all of today's CAD systems are capable of producing an STL file.

The Department of Mechanical and Aerospace Engineering at Carleton University has two prototyping machines: ZCorp Z400 (Z400.Z Corporation, Somerville, Mass., USA) and 1200es Dimension 3D Printer (Stratasys, Inc., Eden Prairie, USA). The Dimension creates solid models out of ABS plastic. The Z400 is capable of generating solid and water-soluble models using a plaster powder and a binder. For this present application, the physical standardized idealized human nasal cavity model was produced using Dimension. The minimum layer thickness of the Dimension 3D printer was 0.25 mm (0.010 inches).

To measure regional as well as total particle deposition efficiencies in the standardized human nasal cavity, the replica was separated into three sections using a similar definition to the one described in section 3.3.1 :

- (i) the anterior/nostril region (32 mm long, from anterior tip of the nostril to anterior maxillary spine landmark);
- (ii) the middle/nasal airway region (64 mm long, from the anterior maxillary spine landmark to the choana);
- (iii) the posterior region (10 mm long, corresponding to the region posterior to the choana known as the nasopharynx).

In addition, anterior and posterior connection pieces were generated to permit connection of the nasal replica to the aerosol generator and outlet pipeline for experiments. Figure 4.1 gives the illustration of the individual parts of Carleton-Civic standardized nasal cavity used for deposition experiments in the ICEM-CAD environment with transparent outer surfaces.

Figure 4.1 Carleton-Civic standardized nasal cavity used for deposition experiments in the ICEM-CAD environment with transparent outer surfaces

Figure 4.2 shows the three regions of the physical model produced using Dimension, along with the two connection pieces. Once all parts of the replica were assembled, they were enclosed in a negative nasal cavity.

Figure 4.2 Carleton-Civic standardized nasal cavity used for deposition experiments: three regions of the physical model along with the two connection pieces

4.2 Experimental apparatus and procedures

The deposition experimental setup is shown in Figure 4.3 The main parts of the experimental setup are as follows:

- 1) Aerosol generator (Model 3450 Vibrating Orifice Aerosol Generator, TSI Incorporated, Shoreview, USA): used to generate monodisperse aerosol from Vitamin E.
- 2) Mixing chamber: helped to ensure complete mixing of the aerosol particles with diluted air in order to reduce the concentration of the aerosol; also allowed the flow rate to be controlled by the introduction of secondary air.
- 3) Particle Size Distribution Analyzer (PSD 3603 Particle Size Distribution Analyzer, TSI Incorporated, Shoreview, USA): used to monitor the aerosol particles sizes and monodispersity.

- 4) Nasal Cavity Model.
- 5) Filter (Marquest Respirgard- II 303 Bacterial filter manufactured by Vital Signs Inc.): used in series at the outlet of the test nasal model to “keep” the oil particles out of nasal passage.
- 6) Vacuum pump, flow meter, pressure gauge, adjustment valve: used to set, monitor and regulate the steady inhalation flow rate. The steady inhalation volume flow rates of 60 and 90 L/min were used in the experiments.
- 7) Solution concentration analyzer (Agilent 8453 UV-visible spectroscopy System, Agilent Technologies, Inc., Waldbronn, USA): used to obtain concentration of Vitamin E from the solution obtained from the washing of nasal model and downstream part.

Figure 4.3 Schematic of experimental apparatus

4.2.1 Aerosol generation

4.2.1.1 The aerosol generator

Liquid material always produces particles with spherical shape and of uniform density because of surface tension (Wen, 1996), thus both geometric diameter and aerodynamic diameter of the particles can be calculated accurately. Aerosols produced with liquid material are highly-monodisperse, with a typical standard deviation better than one percent.

Monodisperse aerosols (i.e., particles with a very narrow size distribution) were generated from Vitamin E oil using a controlled Vibrating Orifice Aerosol Generator (VOAG) (Model 3450, TSI Incorporated, Shoreview, USA), which can produce a high-quality monodisperse aerosol with specific particle size and concentration from any material in solution form. Even though a wide variety of solutions can be used with the Model 3450 VOAG (as shown in Figure 4.4), the monodisperse aerosol generated from Vitamin E was used in this experiment. It dissolved in Isopropyl alcohol, which was adopted as the solvent in present experiment because it has several advantages such as low viscosity and low vapour pressure, easy to work with, and easily evaporates in the drying column.

The jet of liquid was created by pumping the vitamin E (brand Equate®) solution out of a syringe with a stepper motor, into tubing that directs the solution to the orifice. A constant volumetric flow rate was generated by the jet of liquid, and as it passed through the small orifice (with diameters of 5, 10 or 20 μm) it broke into uniform size droplets due to the vibration of the orifice. The orifice vibrated at the same frequency as the

frequency generator because it was in mechanical contact with a piezo-electric ceramic, which was electrically connected to a frequency generator. The frequency of vibration of the orifice can be adjusted from 1 kHz to 1 MHz.

Figure 4.4 TIS Model 3450 Vibrating Orifice Aerosol Generator (left, including the TSI Model 3054 Aerosol Neutralizer) and TIS 3603 Particle Size Distribution Analyzer (right)

4.2.1.2 Aerosol generation principle

When the liquid feed rate and orifice vibration frequency are chosen, the final particle size is determined by the concentration of vitamin E in the isopropyl solution. A run speed of 8.2×10^{-4} cm/s is recommended for a 20 μm orifice with a 20 cm^3 syringe. But

in actual operation, this value can be adjusted to obtain a better particle size distribution. The difficulty in operating the aerosol generator is determining the optimum orifice vibration frequency for producing monodisperse droplets.

For a particular setting (combination of liquid feed rate and orifice vibration frequency) the particle size can be determined by following equation (TSI, 2002):

$$d_p = \left(\frac{6Q_s (C + I)}{\pi f} \right)^{1/3} \quad (4.1)$$

where d_p is the calculated particle diameter; Q_s is the volume flow rate of the jet ($= 5.44 \times 10^{-9} m^3 / s$ for the syringe pump setting of $9.9 \times 10^{-4} cm^3 / s$; 1 % bias limit); f is the vibration frequency of the frequency generator (1% bias limit); C is the volumetric concentration of the solution of vitamin E (brand Equate®) in alcohol ($C = 0.000196 \times$ Absorbance at 285 nm; 2% bias limit) and I is the residue after evaporation volumetric concentration of the alcohol (40 ppm).

4.2.1.3 Operation of aerosol generation

The steps to operate the Model 3450 include:

- (1) Flushing the liquid feed system;
- (2) Eliminating Air Bubbles;
- (3) Starting the liquid jet;
- (4) Tuning the signal generator to the proper operating frequency;
- (5) Installing the aerosol neutralizer;

(6) Adjusting the dispersion and dilution air;

(7) Stopping the liquid jet.

4.2.1.4 The charge neutralizer

Usually, aerosol particles generated using laboratory generators are highly charged, which is undesirable for the researchers because it can affect the deposition size fraction measurements. The level of charge on aerosols can be reduced by means of small bipolar ions. By exposing an aerosol to a source of ionizing radiation, small bipolar ions can be created and a gaseous medium around the particles can be made electrically conductive. The particles can then discharge themselves by capturing ions of the opposite polarity (Liu and Pui, 1974). In present work, the TSI Model 3054 Aerosol Neutralizer (TSI Incorporated, Shoreview, USA) is used, which consists of 10 millicurie of Krypton-85 gas as a radioactive source sealed in a small diameter, thin-walled stainless steel tube placed along the centre of a cylindrical stainless steel container, as shown in Figure 4.4. The β - radiation produced by the radioactive Kr^{85} gas can penetrate through the thin-walled stainless steel tube to ionize the gas molecules outside. The outer stainless steel cylinder performs two functions: to confine the β - radiation produced by the radioactive Kr^{85} gas and to provide the necessary neutralization volume for the aerosol.

4.2.2 The particle size distribution analyzer

Prior to flowing into nasal cavity model, some of the aerosol is fed into the TSI 3603 Particle Size Distribution Analyzer (PSD) (TSI Incorporated, Shoreview, USA), which is

shown in Figure 4.4. Section 4.2.1.2 explained that the particle size can be calculated for a particular setting of the aerosol generator (combination of liquid feed rate and orifice vibration frequency). However, the generated size of particles we generated may be different from the calculated value since each orifice is slightly smaller or larger than the nominal diameter due to manufacturing tolerances. Although this does not have direct effect on the final particle size, it does have an effect on the operating frequency range of a particular orifice, and in turn the operating frequency will affect the size of the generated particle. Although the dispersion and dilution air are adjusted for each run, it is impossible to generate absolutely uniform particles at optimum dispersion airflow. Thus, it is indispensable and necessary to measure and analyze the particle size distribution. PSD 3603 Particle Size Distribution Analyzer was used in our present experiments to measure the aerosol particle size, as well as to ensure the aerosol droplets were monodisperse.

The operational principle of the PSD is described in the manual of this device (TSI, 2004). Air with aerosol from aerosol generator was bled from the mixing chamber at flow rate of 7 L/min into the PSD. Most of the air (with flow rate of 6 L/min) was diverted and filtered, and then re-directed through a nozzle. The rest of the air containing the aerosol (1 L/min) flowed through a smaller inner nozzle, which was installed inside the outer nozzle. The aerosol exited this inner nozzle into the sampling area. Sheath air from the outer nozzle with flow rate of 6 L/min surrounded the aerosol, causing the flow from the inner nozzle to form a central region of more uniform flow. The aerosol particles were accelerated to a high velocity in a narrow stream, and they lagged behind due to their inertia. During this acceleration, particles passed individually through a pair

of overlapping laser beams. Light scattered off the particle from each beam passed through a lens to an avalanche photo-detector, which produced a distinct double-crested electrical pulse. The time between the crests was determined by the drag force on the particle. The air continued into a diffuser and the particles were trapped downstream.

The PSD 3603 is an integrated system for particle size measurement which provides fast, reliable results, and the bias limit of the measurement is 2%. The PSD 3603 works with the Particle Instrument Manager (PIM) software that provides an intuitive user interface and allows for efficient data analysis and regulatory compliance. When data collection is started, the run properties dialog box opens and Size Graph, Size Table, Cumulative Table and Statistics Table are available to show particle statistics, including size range, geometric mean value and geometric standard deviation. By monitoring the size graph, cumulative table and statistics Ttable, it is not difficult to tell whether the aerosol is monodisperse or not. A sample size distribution plot is shown in Figure 4.5 below.

Figure 4.5 Sample particle size graph, $d_p = 4.62\mu\text{m}$

4.2.3 Other parts of the flow system

4.2.3.1 The vacuum pump

A Welch dry vacuum pump Model 2585B (Gardner Denver Welch Vacuum Technology Inc.) was adopted in current measurements to drive the flow. The pump was placed downstream of the mass flow meter and manual control valve. It was capable of pulling about 200 L/min through the system, which was sufficient for the present testing flow rates.

4.2.3.2 The mass flow meter

In the present experiment, the flow rate was measured using the Brooks Instrument Model 5863S Thermal mass flow meter. The principle of operation is based on the equipment manual (Brooks Instrument, 2000). Air was diverted through a bypass channel, where it flowed past a heating element. The power supplied to the heating element was known or constant. The temperature difference between upstream and downstream was measured using two sensing elements, one upstream and one downstream. This temperature difference is proportional to the mass flow rate. The two sensing elements were connected in a bridge circuit. The resistance in each element depends on its temperature. Using the bridge circuit, the difference in resistance between upstream and downstream was determined, which gave the temperature difference. A voltage output signal proportional to the mass flow rate was generated and fed into a National Instruments data acquisition card, which was read by the LabView software.

The maximum flow rate of this flow meter was 150 SLPM (the standard litres per minute of air at a pressure of 101.325 kPa and a temperature of 0 °C), which was sufficient to measure the test flow rate used in the present study. The bias error of the flow meter is 0.2% of the full scale (0.3 SLPM) and 0.7% of the operating range.

4.2.4 Particle deposition measurement

Approximately two hours were required to complete the flow portion of the experimental protocol for detecting particle deposition fraction. Data for several inhalation mass flow rates and particle sizes were collected, and thus the time to achieve detectable levels and sufficient deposition for accurate measurement varied. The protocol was repeated three times for each particle size at each flow rate using a solution with the same concentration of particles to decrease precision uncertainty.

After the flow part of the experiment was finished, the nasal model and the filter were detached from experimental setup and the vitamin E was washed from the three parts of the nasal model and from the filter. Then the amount of vitamin E was measured with the spectrophotometer and the total deposition fraction was calculated.

4.2.4.1 Wash procedure

To measure the amount of deposited Vitamin E in the nasal cavity, the three parts of the standardized nasal model and filter were washed separately with solvents (methanol, typically 10 mL). It was necessary to repeat washing at least five times for each part of

nasal model because of its complex geometry. The filter was soaked in a beaker containing a fixed amount of isopropyl alcohol (typically 10 mL, same as used for the parts of nasal cavity model). The beaker contained the filter pad detached from the filter, and the beaker was shaken for several minutes to allow the Vitamin E to dissolve sufficiently in the methanol.

4.2.4.2 The spectrophotometer

An Agilent 8453 UV-visible Spectroscopy system (Agilent Technologies) shown in Figure 4.6 was used in the present experiment to measure the concentrations of vitamin E in the isopropyl alcohol solutions obtained from the wash procedure. The principle and description of this instrument is based on the instrument manual (Agilent Technologies, 2003).

Figure 4.6 Agilent 8453 UV-visible Spectroscopy system

For one sample, its absorbance peak occurs in the range from 190 nm to 1100 nm in 1 nm increments, and the absorbance (Ab) is defined as:

$$Ab = \log_{10}(\text{Incident light intensity}/\text{Transmitted light intensity}) \quad (4.2)$$

The absorbance peak of Vitamin E occurs at 285 nm and spans a wavelength range of 252-300 nm. The absorbance measured at 320 nm is used as reference and is subtracted from each absorbance measured at 285 nm to correct for impurities in the solution. The absorbance value used to calculate the particle deposition fraction is the wavelength-weighted average over 252-300 nm.

Any uncertainty in the intensity of the transmitted light causes an uncertainty in the absorbance proportional to 10^{Ab} , which grows very quickly when Ab is greater than 1. Therefore, if the measured absorbance at 285 nm was greater than 1.5, the measurement was not used.

The total particle deposition fraction (DF) can be calculated using Equation 4.3:

$$DF = \frac{M_n}{M_n + M_f} \quad (4.3)$$

where M_n and M_f are the masses of particles deposited in the nasal model and in the down-stream filter, respectively. Because the same volume of methanol was used to wash the three parts of nasal model and filter, and the absorption is directly proportional to the concentration of a solution according to Beer's Law (Bauman and Poe, 1962), and the total deposition fraction can also be obtained by:

$$DF = \frac{\sum_{i=1}^3 Vol_{n_i} Ab_{n_i}}{\sum_{i=1}^3 Vol_{n_i} Ab_{n_i} + Vol_f Ab_f} \quad (4.4)$$

where, Vol_n , Vol_f and Ab_n , Ab_f are the volume and absorption of solutions obtained from the washing of nasal model and down-stream filter, respectively.

4.3 Uncertainty analysis

True values of experimental results are seldom known and experiments always have errors due to instruments, data acquisition, data reduction, and environmental effects. It is important to determine the uncertainty for risk assessments in experimental set up design and for using data directly or in calibrating and/or validating simulation methods. In this section, uncertainty analysis will be performed based on the ANSI/ASME Measurement Uncertainty Standard (1985).

(A) Two readings

(B) Infinite number of readings

Figure 4.7 Errors in the measurement of a variable X (Coleman & Steele, 1999)

As illustrated in Figure 4.7, there are two types of uncertainty measures for data: the propagated bias error, and the precision. Bias errors (β) are those due to inability of the equipment to measure true values or the faults in the measuring instruments or in the techniques used in the experiments, thus, they are also called systematic errors. The propagated bias error is the estimate of the influence of all the different sources of bias error on the final measurement. The precision (random) error (ε) is the scatter in the measurements caused by random errors, which are associated with unpredictable variations in the experiment, or are due to a deficiency in defining the quantity being measured. In the following sections, different types of bias errors and precision errors are discussed, estimated separately and then combined together to get the total error (δ).

4.3.1 Bias Error

Strictly speaking, it is not possible to measure the actual bias error of any particular instrument, so actual bias error must be estimated. The estimated bias error is called the bias limit, and it represents the likely range in either the positive or negative direction that contains the true bias. Thus the bias limit is also called symmetric limit. When there are several different bias limits to be combined (for a function $f(x_1, x_2, \dots, x_N)$), it is assumed that there are as many negative bias errors as positive errors, so they can be roughly combined in quadrature by the root sum of squares formula shown in Equation 4.5. When there are only a few bias limits to be combined, the same equation is used, but it is a less certain estimate, since they might actually combine additively. Propagated bias error for a function $f(x_1, x_2, \dots, x_N)$ is calculated according to following formula:

$$\beta = \sqrt{\beta_1^2 + \beta_2^2 + \dots + \beta_N^2} \quad (4.5)$$

where, $\beta, \beta_1, \beta_2, \dots, \beta_N$ are the propagated bias error, bias limit 1, bias limit 2, ..., bias limit N. The bias limits can be calculated using Equation 4.6.

$$B = \frac{\partial f(x_1, x_2, \dots, x_N)}{\partial x_1} \beta_{x1} \quad (4.6)$$

As previously stated, in present experimental research, the total particle deposition in nasal cavity, DF , is defined as function of inertial parameter, IP , that is:

$$DF = f(IP) = f(\rho d_p^2 Q) = f(d_a^2 Q) \quad (4.7)$$

where, ρ (kg/m^3) is the density of particles, d_p (usually in μm) is the geometric diameter of particles, d_a (usually in μm) is the aerodynamic diameter of particles, Q (L/min) is the inhalation flow rate. In the following subsections, bias errors due to different factors will be discussed separately.

4.3.1.1 Inertial parameter

The bias limit of the particle density is a function of the vitamin E used to generate particle. The specific gravity of the vitamin E (brand Equate®) used in present experimental work is 0.92 ± 0.01 . Thus the bias limit of the particle density can be calculated using following equation:

$$\frac{\beta_{\rho_p}}{\rho_p} = \frac{1\%}{0.92} = 1.09\% \quad (4.8)$$

As discussed in the section 4.2.1.2, the particle size was calculated based on the operation of the aerosol generator, thus the bias limit of the geometric diameter of particles can be obtained using equation 4.9:

$$\frac{\beta_d}{d} = \frac{1}{3} \sqrt{\left(\frac{\beta_{Q_s}}{Q_s}\right)^2 + \left(\frac{\beta_f}{f}\right)^2 + \left(\frac{\beta_{C+I}}{C+I}\right)^2} \quad (4.9)$$

For the aerodynamic diameter of particles, the bias limit of the density of the vitamin E must be included in the calculation:

$$\frac{\beta_{d_a}}{d_a} = \frac{1}{3} \sqrt{\left(\frac{\beta_{Q_s}}{Q_s}\right)^2 + \left(\frac{\beta_f}{f}\right)^2 + \left(\frac{\beta_{C+I}}{C+I}\right)^2 + \left(\frac{\beta_\rho}{\rho}\right)^2} \quad (4.10)$$

Prior to being put into the syringe of the aerosol generator (about 2% bias limit in the concentration), the vitamin E solution used to generate aerosols was diluted for measuring the concentration using the spectrophotometer (about 2% bias limit in the concentration). With bias values mentioned in section 4.1.2.1 (Q_s is the volume flow rate of the jet $= 5.44 \times 10^{-9} m^3/s$ for the syringe pump setting of $9.9 \times 10^{-4} cm^3/s$ with 1% bias limit; f is the vibration frequency of the frequency generator with 1% bias limit; C is the volumetric concentration of the vitamin E in alcohol $C = 0.000196 \times$ Absorbance at 285 nm with 2% bias limit), the total bias limit for the calculated aerodynamic diameter can be obtained using equation 4.11:

$$\begin{aligned} \frac{\beta_{d_a}}{d_a} &= \frac{1}{3} \sqrt{\left(\frac{\beta_{Q_s}}{Q_s}\right)^2 + \left(\frac{\beta_f}{f}\right)^2 + \left(\frac{\beta_{C+I}}{C+I}\right)^2 + \left(\frac{\beta_\rho}{\rho}\right)^2 + \left(\frac{\beta_C}{C}\right)^2 + \left(\frac{\beta_C}{C}\right)^2} \\ &= \frac{1}{3} \sqrt{(1\%)^2 + (1\%)^2 + (2\%)^2 + \left(\frac{1\%}{0.92}\right)^2 + (2\%)^2 + (2\%)^2} = 2\% \end{aligned} \quad (4.11)$$

From the definition of inertial parameter, the bias limit in it is then:

$$\frac{\beta_{IP}}{IP} = \sqrt{\left(\frac{2\beta_{d_a}}{d_a}\right)^2 + \left(\frac{\beta_Q}{Q}\right)^2} \quad (4.12)$$

Combining all parameters discussed above together, the bias limit in the inertial parameter (I.P.) can be calculated:

$$\frac{\beta_{IP}}{IP} = \sqrt{\left(\frac{2\beta_{d_a}}{d_a}\right)^2 + \left(\frac{\beta_Q}{Q}\right)^2} = \sqrt{(2 \times 2\%)^2 + (0.72\%)^2} = 2.92\% \quad (4.13)$$

Only the measured sizes are used for the presentation of the final data. It is conjectured that there was much variability in the dilution process, and possibly a higher uncertainty in the calibration constant of concentration versus absorbance than estimated. Thus it should be assumed that there is some uncertainty in the inertial parameter not captured by this uncertainty analysis.

4.3.1.2 Total particle deposition fraction

The total particle deposition fraction, DF , can be calculated by:

$$DF = \frac{\sum_{i=1}^3 Vol_{n_i} Ab_{n_i}}{\sum_{i=1}^3 Vol_{n_i} Ab_{n_i} + Vol_f Ab_f} = \frac{\sum_{i=1}^3 N_{n_i}}{\sum_{i=1}^3 N_{n_i} + N_f} = \frac{N_n}{N_n + N_f} \quad (4.14)$$

where, Vol_n , Vol_f and Ab_n , Ab_f are the volume and absorption of solutions obtained from the washing of nasal model and down-stream filter, respectively. The bias limit of DF is:

$$\beta_{DF} = \sqrt{\sum_{i=1}^3 \left(\beta_{N_{n_i}} \frac{\partial DF}{\partial N_{n_i}} \right)^2 + \left(\beta_{N_f} \frac{\partial DF}{\partial N_f} \right)^2} \quad (4.15)$$

$$\frac{\partial DF}{\partial N_n} = \frac{N_f}{(N_n + N_f)^2} = \frac{\frac{N_f}{N_n} N_n}{(N_n + N_f)^2} = DF(1 - DF) \frac{1}{N_n} \quad (4.16)$$

$$\frac{\partial DF}{\partial N_f} = \frac{-N_n}{(N_n + N_f)^2} = DF(1 - DF) \frac{-1}{N_f} \quad (4.17)$$

$$\frac{\beta_{DF}}{DF} = (1 - DF) \sqrt{\left(\frac{\beta_{N_n}}{N_n} \right)^2 + \left(\frac{\beta_{N_f}}{N_f} \right)^2} \quad (4.18)$$

$$\frac{\beta_{DF}}{DF} = (1 - DF) \sqrt{\sum_{i=1}^3 \left(\frac{\beta_{Vol_{n_i}}}{Vol_{n_i}} \right)^2 + \left(\frac{\beta_{Vol_f}}{Vol_f} \right)^2 + \sum_{i=1}^3 \left(\frac{\beta_{Ab_{n_i}}}{Ab_{n_i}} \right)^2 + \left(\frac{\beta_{Ab_f}}{Ab_f} \right)^2} \quad (4.19)$$

Some estimates have been made to calculate the bias of total particle deposition fraction:

$$\frac{\beta_{Vol_{n_i}}}{Vol_{n_i}} = 1.4\% \quad (4.20)$$

$$\frac{\beta_{Vol_f}}{Vol_f} = 4.3\% \quad (4.21)$$

$$\frac{\beta_{Ab_{n_i}}}{Vol_{Ab_{n_i}}} = \frac{\beta_{Ab_f}}{Vol_{Ab_f}} = 2\% \quad (4.22)$$

Then, the bias limit of the total particle deposition fraction can be calculated by:

$$\begin{aligned} \frac{\beta_{DF}}{DF} &= (1 - DF) \sqrt{\sum_{i=1}^3 (1.4\%)^2 + (4.3\%)^2 + \sum_{i=1}^3 (2\%)^2 + (2\%)^2} \\ &= 6.35\%(1 - DF) \end{aligned} \quad (4.23)$$

In summary, the bias limits of the key parameters in the present experiment are summarized in Table 4.1.

Table 4.1 Bias limits of the key parameters of total particle fraction measurement

Parameter	Bias limit
d_a	2.0%
Q	0.72%
$I.P.$	2.92%
DF	6.35%(1- DF)

4.3.2 Precision

The precision error is random error and is different for every reading, and hence cannot be removed. It causes scatter in the total particle deposition fraction results of different experiments for the same experimental parameters (particle size and inhalation flow rate). In present experimental research, total particle deposition (DF) for three inhalation flow rates (90, 60, 30 L/min) was studied. For each flow rate, 5~7 data points (supposedly with the same particle diameter and impaction parameter) were used. Three measurements were performed for each data point. When different experiments at the same data point have different particle diameters or impaction parameters, the average particle diameters and impaction parameters are used. The error caused by this is accounted for in the precision error. The precision limit of the measured results can be calculated using following equations:

$$P_{\bar{r}} = \frac{tS_{\bar{r}}}{\sqrt{M}} \quad (4.24)$$

$$S_{\bar{r}} = \left[\sum_{k=1}^M \frac{(r_k - \bar{r})^2}{M-1} \right]^{1/2} \quad (4.25)$$

$$\bar{r} = \frac{1}{M} \sum_{k=1}^M r_k \quad (4.26)$$

where, t is the coverage factor, $S_{\bar{r}}$ is the standard deviation for M readings of the results, and $\bar{r}$ is the averaged result.

For example, for the data point with inhalation flow rate of 60 L/min, particle diameter of 4.69 μm and an impaction parameter of 1214.34, the three readings gave an averaged total particle deposition fraction of 0.55 with a standard deviation of 0.0166. The t -value for 2 freedom degree and a 95% confidence interval was 4.32, thus the uncertainty for this data point can be calculated: $P_{\bar{r}} = \frac{tS_{\bar{r}}}{\sqrt{M}} = \frac{4.32 \times 0.166}{\sqrt{3}} = 0.041 = 4.1\%$.

4.3.3 Total uncertainty

As discussed above, the bias error and precision error of the total particle deposition fraction can be determined. The total uncertainty of the total particle deposition fraction is the root sum of squares of the precision error and the bias error. Then the total uncertainty for each average result can be calculated using:

$$U_{\bar{r}}^2 = B_{\bar{r}}^2 + P_{\bar{r}}^2 \quad (4.27)$$

For example, using the same data point discussed in the previous section with inhalation flow rate of 60 L/min, particle diameter of 4.69 micron, impaction parameter of 1214.34, the bias error is 0.009, and the precision is 0.041, there is a total uncertainty

of $\sqrt{0.009^2 + 0.041^2} = 0.044$. The detailed precision error, bias error and total uncertainty of experimental results as well as further discussion of the experimental results will be given in the following chapter.

Chapter 5: Experimental Deposition Results

5.1 Measured and simulated total particle deposition fraction

The total deposition of particles (DF) in the nasal cavity is a function of particle size and respiratory patterns. As mentioned in section 2.2, it is common to define an impaction parameter $d_a^2 Q = \rho_p d_p^2 Q$ to analyse particle deposition fraction, where d_a is the aerodynamic diameter of particles (usually in μm), ρ_p is the particle density in g/cm^3 , d_p is the particle diameter in μm , and Q is the inhalation flow rate in L/min .

5.1.1 *Measured total particle deposition fraction*

The experimental results of total particle deposition fraction in the standardized nasal cavity, along with the calculated experimental uncertainties, are summarized in Table 5.1. Total absolute uncertainties in measured deposition fraction ranged from 0.011 to 0.063 (4.2 to 29.5 % of the measured deposition fraction). It can be seen that for each flow rate, the total particle deposition fraction increase as the inertial impaction parameter increase. The trajectories of particles with large inertia are greatly determined by inertial forces and tend to deviate from flow streamlines. Thus, particles with large inertia deviate from flow streamlines, impact into airway surfaces and then deposit there.

In following sections, the current experimental data of the standardized human nasal cavity are compared with compared with *in vivo* and *in vitro* data of other researchers.

As shown in , the current data are plotted in for flow rates of 30, 60, and 90 L/min, with two-dimensional error bars representing calculated total experimental uncertainties in both deposition fraction and impaction parameter.

Table 5.1 Experimental Results and Uncertainty

Flow Rate (L/min)	Particle Size (μm)	Impaction Parameter ($\mu\text{m}^2 \text{ L/min}$)	Total Deposition Fraction	Bias Limit	Precision Uncertainty	Combined Uncertainty
90	5.00	2070.1	0.857	0.007	0.036	0.036
	3.61	1080.1	0.533	0.016	0.061	0.063
	3.06	772.8	0.423	0.016	0.041	0.044
	2.49	511.5	0.237	0.012	0.039	0.040
	1.74	250.8	0.116	0.007	0.028	0.029
60	6.77	2527.6	0.830	0.008	0.039	0.040
	5.75	1823.0	0.690	0.013	0.029	0.032
	4.69	1214.3	0.521	0.016	0.032	0.036
	3.14	542.6	0.215	0.011	0.047	0.048
	2.57	363.2	0.178	0.010	0.017	0.020
	1.71	162.1	0.083	0.005	0.013	0.014
30	9.14	2305.7	0.790	0.011	0.047	0.048
	8.20	1855.8	0.644	0.015	0.044	0.046
	6.34	1110.1	0.473	0.016	0.042	0.045
	5.23	756.2	0.332	0.014	0.046	0.048
	3.09	263.5	0.102	0.006	0.032	0.032
	2.11	123.3	0.061	0.004	0.010	0.011

5.1.1.1 Comparison with *in-vivo* data

In Figure 5.1, data are compared with *in vivo* measurements of Landahl and Black (1947), Pattle (1961), Hounam *et al.* (1969), Giacomelli-Maltoni *et al.* (1972), and Heyder and Rudolf (1977). The solid line from Cheng (2003) representing the empirical fit to cited *in vivo* data is also showed for comparison purpose.

It is worth noting from Figure 5.1 that the *in vivo* data scatter in a significant range, especially considering that data are plotted on semi-log axes. Results for present *in vitro* measurements using the Carleton-Civic standardized model effectively capture the sigmoid trend but fall on the lower bound of the scattered *in vivo* data.

Figure 5.1 Experimental results of total particle deposition fraction compared with published *in vivo* data

This difference is not unexpected because of the different principles of *in vivo* and *in vitro* measurements. *In vivo* data are typically derived from concentration measurements

before inhalation into the nose and after exhalation through the mouth (Landahl and Black, 1947; Pattle, 1961; Hounam *et al.*, 1969; Giacomelli-Maltoni *et al.*, 1972; Heyder and Rudolf, 1977), and as such calculated depositions fractions from *in vivo* measurements would include any additional deposition in the nasopharynx and in the oral cavity. Moreover, in *in vivo* experiments, the presence of hairs in the nostrils would increase particle filtration, particularly for larger particles (see Landahl and Tracewell, 1949; Scott *et al.*, 1978; Swift and Kesavanathan, 1996). Finally, differences in nasal cavity “wall roughness” between the hard surfaced *in vitro* replicas and actual human subjects might also affect deposition

5.1.1.2 Comparison with published *in vitro* data

As shown in Figure 5.2, measured data in the standardized nasal cavity are compared with published *in vitro* results from Swift (1991), Lennon *et al.* (1998), Zwartz and Guilmette (2001), Cheng *et al.* (2001), Kelly *et al.* (2004), and Garcia *et al.* (2009). The semi-empirical fit line to cited *in-vivo* data, as summarized by Cheng (2003), is also shown for comparison. With the exception of the data from Swift (1991), which were obtained using a hand-carved replica, all of the *in vitro* data follow a similar trend, which itself falls below the summary *in vivo* curve. Thus, the difference between *in vivo* and *in vitro* derived data is consistent in the literature, and is attributable to the combination of effects cited in Section 5.1.1.1.

Observing *in vitro* data only, the current measured deposition results for the standardized geometry cross through the bulk of the available data, while showing comparatively less deposition at high values of the inertial impaction parameter (i.e. $d_a^2 Q$)

> 1000). Given the range of different flow rates and particle sizes among these *in vitro* data sets, the relative lack of scatter in deposition fraction when plotted against the inertial parameter, confirms that inertial impactation is the dominant mechanism of particle deposition.

Figure 5.2 Experimental results of total particle deposition fraction compared with published *in vitro* data

While the agreement among different data sets for different geometries is reasonable given the complexity of the measurements, there are several potential reasons why these results may vary. First is the issue of experimental uncertainty. For the current work,

⊕

total experimental uncertainties are indicated with vertical error bars. Although detailed uncertainty estimates have not generally been reported in the literature, by considering repeated measurements by different researchers using the same geometry, it is possible to qualitatively estimate their significance. In Figure 5.2, all of the data points shown in blue were obtained by a variety of researchers using geometries derived from the same set of CT scans for a single human subject originally reported by Swift (1991). These include the SLA and Viper models of Kelly et al. (2004), the first model of Garcia et al. (2009), and the models of Zwartz and Guilmette (2001), Cheng *et al.* (2001), and Swift (1991). As discussed in Section 2.3.2.2, differences in measured deposition fraction among these studies can be attributed to a combination of experimental uncertainties and variations in wall roughness due to different manufacturing methods (Kelly et al., 2004). The span of these previous *in vitro* data is not insignificant, suggesting that experimental uncertainties (including wall roughness effects) must be acknowledged when comparing different data sources.

Variation in deposition patterns could also be expected among *in-vitro* models derived from different geometries. The latter three models of Garcia et al. (2009) and the model of Lennon et al. (1998) originate from different subjects and thus also reflect inter-subject variability. Focusing just on data from subjects 2-4 of Garcia et al. (2009), for which any potential systematic errors should be consistent, the variability among these subjects spans the main data band in Figure 5.2. Considering also the data from Lennon et al. (1998), it can be seen that inter-subject variability is likely the dominant source of scatter, which highlights the role and significance of our novel standardized geometries in research. Ideally, one would hope that the *in vitro* deposition data for the standardized

model would fall on the center of data derived from these different individuals. However, since the number of different subjects represented in the available cited data is still quite small (i.e. 5 individuals), and effects of inter-subject variability in these data are quite significant, the level of agreement is not unreasonable.

Finally, besides issues of uncertainty, wall-roughness, and inter-subject variability, there is still the possibility that the variance in deposition fraction at high values of the impaction parameter is in fact statistically significant, and that some aspect of the standardized geometry itself results in difference. Nevertheless, it is reassuring that the data from the standardized model crosses through the bulk of the published *in vitro* data while showing a similar sigmoid trend as noted above.

5.1.2 Measured regional particle deposition fraction

In addition to total particle deposition fraction, regional distribution of deposited particles in the human nasal cavity is very important when studying nasal drug delivery. As detailed in the discussion of the experimental apparatus, the physical replica was split into three parts so that regional deposition data could be collected and analyzed. The regions were designed based on the physiology of nasal cavity, and were not of equal size. The anterior region included the parts of the nose and passageways up to the nasal valve; the middle region included the turbinates up to the choana, and the posterior region included the small region in the vicinity of the nasopharynx up to the end of the model.

Figure 5.3a-c shows the measured regional particle deposition fraction for inhalation flow rates of 30, 60, and 90 L/min. Despite the different flow rates, the regional particle deposition fraction has the same trends for anterior, middle and posterior sections of the

cavity. Particle deposition fraction in the anterior part of nasal cavity increases with increasing particle size, and is the major part of the total deposition fraction. For the middle region, the peak deposition occurs when the impaction parameter is equal to approximately $1500 \text{ mm}^2\text{L/min}$. For the posterior section, the deposition fraction does not vary significantly with impaction parameter and is sufficiently small that it can be neglected. Further discussion of the measured regional deposition fraction (including comparison with simulated results) is shown in Chapter 7.

Figure 5.3 Experimental measurements of regional particle deposition fraction in the Carleton-Civic standardized nasal cavity geometry

Chapter 6: Numerical Simulation Methodology

6.1 Theory

6.2 The motion of particles

To estimate the net force on an immersed particle, we consider all individual component forces, which may arise from pressure gradients and relative motion of the fluid and particle, and may be functions of position, velocity, and acceleration. These forces are summarized in Table 6.1, where V is the volume of the body, ρ is the density of the fluid, $A_D = C_D A$ is the drag area, C_D is the steady drag coefficient, A is the projected area of the object, $(a_F)_G$ is the acceleration of fluid relative to Earth and $(a_F)_B$ is the acceleration of fluid relative to the body. It is also possible that the rate of change of acceleration could influence the net force, or even higher motion derivatives might be significant.

Table 6.1 Force exerted on immersed objects

Pressure Gradient	1. $B_I = \rho V g$	2. $B_2 = -V(dp/dx)$	3. $A_2 = \rho V(a_F)_{0G}$
Relative Motion		4. $D = 0.5\rho(u_F)^2_B A_D$, etc.	5. $A_I = m_a(a_F)_B$

Force type 1 exists in the absence of particle and fluid motion, which is the familiar buoyancy force $B = \rho V g$ arising from the pressure gradient ρg caused in the fluid by gravity. Force type 2 and 3 also arise from pressure gradients in the fluid, but type 2 arises from friction, e.g. on the walls of a wind tunnel, but not on the object itself, and type 3 arises from the pressure gradient in the bulk fluid. These two forces are also called buoyancy forces and all the type 1, 2 and 3 results in the concept of generalized buoyancy. Type 4 represents the forces arising directly from the velocity of the fluid

relative to the selected free body, $(\frac{1}{u_F})_B$. These include forces like lift and drag (roughly dependent on u^2), or the viscous damping force used in vibration analysis (proportional to u). Additionally, turbulent dispersion force also belongs to this type of force. These are only important for small objects (such as water drops smaller than $100 \mu m$ in air). Turbulent dispersion force brings additional dispersion of particles from regions with high volume fraction to regions with low volume fraction because of turbulent fluctuations. The type 5 force is composed of forces that arise from changes of $(\frac{1}{u_F})_B$, i.e., acceleration of the fluid relative to the free body. This type of force can arise from an absolute acceleration of the object or of the fluid, or sometimes both at once.

When an object moves within a fluid, the fluid moves around the object, and then the fluid itself must have kinetic energy. If the speed distribution in the fluid is known, then we can calculate the velocity field of the fluid and obtain the kinetic energy of the fluid. For the idealized case of zero viscosity, an object has no drag, the velocity field and the kinetic energy of the fluid can be determined. The fluid kinetic energy of a moving object, for which the surrounding fluid speed is directly proportional to the object speed, is directly proportional to the object kinetic energy, and can be defined by following equation:

$$K = \frac{1}{2}mu^2 + \frac{1}{2}m_a u^2 \quad (6.1)$$

where, the empirical constant m_a is the added mass, or the added inertia.

Provided that the acceleration of the fluid relative to the free body is used, we obtain:

$$A_1 = m_a (a_F)_B \quad (6.2)$$

In practice, this is often quoted as the added-mass coefficient,

$$C_a = \frac{m_a}{\rho V} \quad (6.3)$$

where, ρ is the fluid density and V is the displacement volume of the object, i.e., ρV is the true mass of fluid displaced by the object. The added mass coefficient C_a for a sphere is 0.5.

Figure 6.1 Drag coefficient (Lapple and Shepard, 1940)

Drag force is a force parallel to the fluid velocity, which the fluid exerts over the body and is given by,

$$D = \frac{1}{2} C_D \rho (u_F)_B^2 A \quad (6.4)$$

where, C_D is the drag coefficient. Figure 6.1 6.1 shows the drag coefficient of spheres, disks and cylinders as a function of the particle's Reynolds number (Lapple and Shepard, 1940).

For a particle with a Reynolds number less than 1, Stokes found that the drag force is,

$$D = 6\pi a\mu U \quad (6.5)$$

where, a is the radius of the sphere, U is the relative velocity between the sphere and the fluid. For sparsely distributed spherical particles, several empirical correlations are available, and Schiller and Naumann (1933) proposed,

$$C_D = \frac{24}{Re} (1 + 0.15 Re^{0.687}) \text{ for } 0 < Re \leq 800 \quad (6.6)$$

which is available in ANSYS CFX (Canonsburg, PA) and is adopted in the present study.

6.2.1 Particle equation of motion

Based on Newton's second law, the acceleration of a particle is proportional to the resultant of all the forces acting on the particle:

$$\sum \vec{F} = m\vec{a} \quad (6.7)$$

Basset (1888) and Ossen (1927) applied Newton's second law of motion and derived an equation for a particle moving under the influence of gravity in a turbulent fluid at rest. Tchen (1947) extended their work and proposed an equation of motion for a small rigid spherical particle in a moving fluid:

$$\begin{aligned} \frac{\pi}{6} d_p^3 \rho_p \frac{du_p}{dt} = & 3\pi\mu d_p (u_f - u_p) - \frac{\pi}{6} d_p^3 \rho_f \frac{du_f}{dt} + \frac{1}{2} \frac{\pi}{6} d_p^3 \rho_f \left(\frac{du_f}{dt} - \frac{du_p}{dt} \right) \\ & + \frac{2}{3} d_p^2 \sqrt{\pi\mu\rho_f} \int_{t_0}^t \frac{du_f/dt' - du_p/dt'}{\sqrt{t-t'}} dt' + \frac{\pi}{6} d_p^3 (\rho_f - \rho_p) g \end{aligned} \quad (6.8)$$

where

d_p = the diameter of the particle

u_p = the velocity of the particle

u_f = the velocity of the fluid phase

ρ_p = the density of the particle

ρ_f = the density of the fluid phase

t_0 = the starting time

μ = the viscosity of fluid phase

In Equation 6.8, the term on the left-hand side of the equal sign is the force required to accelerate the particle. The first term on the right-hand side of the equal sign is the linear viscous resistance force according to Stoke's law. The second term represents the resultant of the pressure gradient in the fluid surrounding the particles, which is a direct effect of the fluid acceleration. The third term represents the surplus of inertia caused by the pressures resulting from the relative acceleration. This term is equivalent to the inertia of the virtual, "added" mass attached to the particle. The fourth term is usually called the "Basset" term and takes into account the effect of the deviation in flow pattern from steady state. It gives the force due to the history of the particle; thus, it is also

called the history term. The last term is due to the external potential force (usually the gravitational force).

There are several assumptions made for the derivation of Equation 6.8:

- (1) The turbulence of fluid field is homogeneous, steady;
- (2) The domain of turbulence is infinite;
- (3) The particle is spherical and follows Stokes's Law;
- (4) There is no mutual action between particles; and
- (5) The diameter of particle must be many times smaller than the Lagrangian eddy length scale as given by equation (6.17).

Several authors extended Tchen's work and proposed other equations. Corrsin and Lumley (1956) modified Tchen's equation by including a term for turbulence pressure gradients. Maxey and Riley (1983) developed equations of motion for a small rigid particle with relative motion of low Reynolds number in a non-uniform flow.

Equation 6.9 is the equation of motion of particle for finite Reynolds number proposed by Mei (1996):

$$\begin{aligned} \frac{4}{3}\pi a^3 \rho_p \frac{dV}{dt} = & \frac{4}{3}\pi a^3 (\rho_f - \rho_p)g + 6\pi\mu a \phi(\text{Re})(U - V) \\ & + 6\pi\mu a \int_{t_0}^t K(t - \tau) \frac{d(U - V)}{d\tau} d\tau + \frac{2}{3}\pi a^3 \rho_f \left(\frac{DU}{Dt} - \frac{dV}{dt} \right) + \frac{4}{3}\pi a^3 \rho_f \frac{DU}{Dt} \end{aligned} \quad (6.9)$$

where V and U are the instantaneous and local velocities of the particle and fluid, respectively; a is the radius of particle and g is the gravitational acceleration. In Equation 6.9, the first term on the right-hand side is the body force (gravity minus buoyancy force); the second term is the drag force; the third term is the Basset history

force; the forth term is the added-mass force and the fifth term is the force due to the fluid pressure gradient and viscous stresses. External forces can be added to the above equation, such as the Saffman lift force due to the velocity gradient transversal to the particle's direction (Saffman, 1965) and the lift force due to the rotation of the particles (Magnus effect).

Considering particles in the range of 0.354 to 16.0 μm with low density ratios ($\rho_f / \rho_p \ll 1$ - making several terms negligible in the particle equation of motion) and taking into account only viscous drag and gravity, the following three-dimensional Lagrangian equations describing the movement of a particle in a Cartesian coordinate system are adopted for the present simulation (Maxey and Riley, 1983; Kim *et al.*, 1998; Mei, 1996; Matida *et al.*, 2004):

$$\frac{du_p}{dt} = \frac{(u_f - u_p)}{\tau_p / \alpha}, \quad (6.10)$$

$$\frac{dv_p}{dt} = \frac{(v_f - v_p)}{\tau_p / \alpha}, \quad (6.11)$$

$$\frac{dw_p}{dt} = \frac{(w_f - w_p)}{\tau_p / \alpha} - g \left(1 - \frac{\rho_f}{\rho_p} \right), \quad (6.12)$$

where the particle relaxation time (the time a particle with an initial velocity, U_{p0} , would travel through a stagnant fluid under the conditions of Stokes drag) is

$$\tau_p = \frac{\rho_p d_p^2}{18\mu_f} \quad (6.13)$$

and

$$\alpha = 1 + 0.15 \text{Re}_p^{0.687} \quad (6.14)$$

where Re_p is the particle's Reynolds number.

6.3 Simulation approach

6.3.1 *RANS/EIM approach*

6.3.1.1 *Averaged Navier-Stokes Equations (RANS)*

The time averaged continuity equation and momentum equations are given by:

$$\frac{\partial \rho}{\partial t} + \rho \frac{\partial \bar{U}_i}{\partial x_i} = 0. \quad (6.15)$$

$$\frac{\partial \bar{U}_i}{\partial t} + \bar{U}_j \frac{\partial \bar{U}_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial \bar{P}}{\partial x_i} + \frac{1}{\rho} \frac{\partial}{\partial x_j} \left(\mu \frac{\partial \bar{U}_i}{\partial x_j} + \mu \frac{\partial \bar{U}_j}{\partial x_i} - \overline{\rho u_i u_j} \right) \quad (6.16)$$

where the new term, $\overline{\rho u_i u_j}$, is called the Reynolds stress tensor. The number of unknowns (ten: three velocity components, pressure, and six stresses) is larger than the number of equations (four: the continuity equation and three components of the Navier-Stokes equations), which leads to a closure problem. Therefore, the Reynolds stress term has to be obtained through modeling.

6.3.1.1.1 *k- ω SST (Shear Stress Transport) Model*

As mentioned in Table 1.1, airflow in the human nasal cavity is highly complex and in the laminar to turbulent flow regimes. In order to capture the airflow structures in the human nasal cavity, the *k- ω SST (Shear Stress Transport)* model was selected here. SST is a blend between *k- ω* near the wall and *k- ε* at the core of the domain. The standard *k- ω* model is used in the prediction of most turbulent flow calculations because of its robustness, economy, and reasonable accuracy for a wide range of flows. However, the

model performs poorly when faced with non-equilibrium boundary layers. It tends to predict the onset of separation too late and to under-predict the amount of separation. Separation influences the overall performance of many devices, and also has a strong influence on other effects, such as wall heat transfer and multi-phase phenomena. This is undesirable and in order to solve the problem, a blending between $k-\omega$ near the wall and $k-\varepsilon$ at the core of the domain was developed. The $k-\omega$ based SST model accounts for the transport of the turbulent shear stress and gives highly accurate predictions of the onset and the amount of flow separation under adverse pressure gradients. The governing equations of the SST model are described in Appendix A.

6.3.1.2 Eddy Interaction Model (EIM)

The Eddy interaction model (EIM), as shown in Figure 6.2, is a Lagrangian method of simulation used to numerically track liquid or solid particles released in turbulent flows. In EIMs, (Zhou and Leschziner, 1991; Wang and Stock, 1992; Graham and James, 1996; Hennick and Lightstone, 2000), it is assumed that one particle is allowed to interact successively with various eddies, which means a particle is always within a single turbulent eddy. Each eddy has its characteristic lifetime, length, and velocity scale from the primary flow calculation results. The end of interaction between the particle and one eddy occurs when the lifetime of the eddy is over or when the particle crosses the eddy. At this instant, a new interaction with the particle and a new eddy is started. The trajectory of this particular particle is obtained by solving the particle equation of motion. In order to obtain velocity or deposition statistics, hundreds of particles must be released into the flow. The local fluctuating velocities are obtained by multiplying the root-mean

square (RMS) fluid fluctuating velocity by random numbers (N_u , N_v , N_w) generated from a Gaussian probability density function of zero mean and unity standard deviation at the start of one eddy-particle interaction. The random numbers are maintained constant during one eddy interaction, while respective RMS values are varied according to the particle position (see MacInnes and Bracco, 1992).

Figure 6.2 Eddy-particle interaction model

6.3.1.2.1 Characteristic length, time and velocity scales of fluid eddies

On the basis of the method of Gosman and Ionannides (1981), Schuen *et al.* (1983) simulated the particle dispersion in a turbulent round jet, where they used a $k-\epsilon$ turbulence model along with the following characteristic length, time and velocity scales of fluid eddies:

$$L_e = C_\mu^{3/4} \frac{k^{3/2}}{\varepsilon} \quad (6.17)$$

$$\tau_e = \frac{L_e}{(2k/3)^{1/2}} \quad (6.18)$$

$$u_e = \left(\frac{2k}{3} \right)^{1/2} \quad (6.19)$$

where, k is the local turbulent kinetic energy, ε is the turbulent viscous dissipation, and C_μ is a turbulence constant, which was chosen to relate the characteristic length scale to the eddy dissipation length (Hinze, 1975). During one eddy-particle interaction, τ_e remains constant.

Although lifetime scales, τ_e , can be randomized using an exponential probability density function, Graham and James (1996) pointed out that in the case when lifetime scales τ_e are specified to be constant in time, the choice of $\tau_e = 2\tau_L$ ensures dispersion consistency. Here τ_L is the Lagrangian fluid time scale. Graham and James (1996) also concluded that to reduce computational costs, the constant eddy lifetime scheme is preferred over an exponentially decaying lifetime scheme.

Considering that the Lagrangian and the Eulerian integral time scales are proportional in homogeneous isotropic stationary turbulence (HIST), Kallio and Reeks (1989) have estimated the Lagrangian integral time scales by,

$$\tau_L = \beta \tau_e \cong 0.8 \beta \frac{k}{\varepsilon} \quad (6.20)$$

Here, β is a function of the turbulent Reynolds number ($\text{Re}_\lambda = u'\lambda/\nu$), varying from 0.6 to 0.3 for $\text{Re}_\lambda = 20$ to 70, according to Sato and Yamamoto's (1987) measurements.

Hinze (1975) has proposed β being approximately 0.4. According to Hinze (1975), the Lagrangian time scale is the largest interval in time that a Lagrangian particle will continue moving in that direction.

Since the particles used in the present calculation are relatively small, crossing trajectory effects are not relevant and the length scales can be neglected (Matida, 2000). The following characteristic scale of fluid eddies are used:

$$\tau_e = 2\tau_L = 0.2k / \varepsilon \quad (6.21)$$

for the time scale, with τ_e maintained constant during one eddy-particle interaction and

$$u_e = \left(\frac{2k}{3} \right)^{1/2} \quad (6.22)$$

for the eddy characteristic velocity scale.

6.3.1.2.2 Local fluctuation velocities of the eddy

The fluid velocity components in Equations 6.12–6.14 are instantaneous quantities composed of the mean part and the fluctuating part; for example:

$$u_f = U_f + u'_f \quad (6.23)$$

The local fluctuation velocities of the eddy are generated at the start of each interaction and are given as follows:

$$(u'_f, v'_f, w'_f) = (N_u u'_{rms}, N_v v'_{rms}, N_w w'_{rms}) \quad (6.24)$$

where, $u'_{rms}, v'_{rms}, w'_{rms}$ are the RMS values of the fluctuating velocities, N_u, N_v and N_w are the random numbers generated from a Gaussian probability density function of zero mean and unity standard deviation. In the present work, for the sake of simplicity, the isotropic decomposition of the turbulence is adopted:

$$u'_{rms} = v'_{rms} = w'_{rms} = \left(\frac{2k}{3} \right)^{\frac{1}{2}} \quad (6.25)$$

Strictly speaking, the word random is reserved for the output of a random physical process, like the time between clicks of a Geiger counter placed next to a radioactive element. The term quasi-random is sometimes used for computer-generated sequences, which will be entirely predictable, hence not truly “random”. There are many statistically well-tested “random number generators” available in the literature (see Press *et al.*, 1989 and Knuth, 1981), such as uniform deviates, exponential deviates and normal (Gaussian) deviates, that can be used with some confidence.

6.3.2 Large eddy simulation

In addition to the RANS/EIM approach, the standard LES particle simulation is also performed on the same grid (4,000,000 elements) for comparison purposes. Large eddy simulation (LES) is a technique intermediate between the direct numerical simulation (DNS) of turbulent flows and the solution of the Reynolds-averaged equations (RANS). In LES, the contribution of the large, energy-carrying structures to momentum and energy transfer is computed exactly, and only the effect of the smallest scales of turbulence is modeled. Since the small scales tend to be more homogeneous and

universal, and less affected by the boundary conditions than the large ones, there is hope that their models can be simpler and require fewer adjustments when applied to different flows than similar models for the RANS equations.

LES is very similar to Direct Numerical Simulation (DNS) in that it provides a three-dimensional, time dependent solution of the Navier-Stokes equations. Thus, fairly fine meshes are still required for LES. However, LES can be used at much higher Reynolds numbers than DNS. Ideally, in fact, if the small scales obey inertial-range dynamics, the cost of a computation is independent of Re (not, however, if a solid boundary is present). The standard subgrid scale model proposed by Smagorinsky (1963) and Lilly (1996) with a wall damping function is used here. The filtered equations are shown in Appendix B.

The simulation was initialized from a converged RANS velocity field as described in the previous section 6.3.1. In present work, “Frozen-domain” particle tracking method was used. Contrary with the dynamic LES (in which several groups of particles are released at different time steps, and are tracked over time), “Frozen-domain” is a three-dimensional fluid domain whose values of the velocity are kept as the instantaneous values at the particular time step when the tracking begins. Thousands of particles were released and fully tracked in one iteration in a “frozen” LES computational domain and deposition statistics were gathered. This “frozen” calculation was made possible (in CFX 11.0) by tracking all particles in a single steady-mode iteration without any eddy interaction model. The reason for adopting the “Frozen-domain” particle tracking method here is that, when compared with the dynamic LES particle tracking approach, it is much more economical while yielding results very similar to those of the dynamic tracking approach (Breuer et al., 2006).

6.4 Simulation domain and method

6.4.1 *Generation of mesh*

The Carleton-Civic standardized nasal model was meshed using ICEM-CFD (Ansys, Inc.). The surface and volume mesh were initially generated using tetrahedral elements and subsequently three layers of prismatic elements were created near the wall using 10% of the size of tetrahedral elements as initial height and 1.2 as the height ratio.

Figure 6.3 Sample of tetrahedral and prismatic elements for 4 000 000 elements

The numerical accuracy can be enhanced with a highly refined mesh density of prismatic layers along the walls. Analysis of grid convergence was performed by considering pressure drop, mean velocity distribution at an arbitrary location and particle deposition for four different grid sizes (approximately 300 000, 1 000 000, 2 000 000 and 4 000 000 tetrahedral and prismatic elements). The sample surface mesh at the outlet for the mesh with 4 000 000 total elements number is shown in Figure 6.3, in which some mesh elements were magnified for the sake of clarity.

6.4.2 *Boundary conditions setting*

The numerical simulations were carried out with a commercial finite-volume based program, i.e., CFX 11 from Ansys INC. (Canonsburg, PA). The following conditions were assumed before computation for sake of simplification:

- (1) steady inhalation flow of pure air;
- (2) incompressible, isothermal air 25°C dry, steady-state;
- (3) constant geometry with hydraulically smooth walls (no vasomotor changes);
- (4) no nasal hair or mucous membranes;
- (5) one-way coupling approach for the particulate phase, because a dilute suspension was used in the experiments.

6.4.2.1 *Boundary conditions setting for RANS/EIM approach*

The basic boundary conditions for RANS/EIM approach were explained in the following paragraphs.

Inlet: Five different volume flow rates were chosen in performing the simulation: 90 L/min, 60 L/min, 45 L/min, 30 L/min, and 15 L/min. For the k - ε turbulence model and Reynolds stress models, the inlet turbulence quantities, k and ε , were either specified directly or calculated using expressions that scale the distribution at the inlet according to the turbulence intensity, I , where:

$$I = \frac{u}{U} \quad (6.26)$$

There are several options to set the fluid values for the calculation domain when using CFX software, such as: turbulence intensity and length scale, intensity and eddy viscosity ratio, k and ε , or intensity and auto compute length. When the turbulence intensity and length scale are both specified, the turbulence kinetic energy and dissipation are calculated using Equation 6.27 and Equation 6.28:

$$k_{inlet} = \frac{3}{2} I^2 U^2 \quad (6.27)$$

and

$$\varepsilon_{inlet} = \frac{k_{inlet}^{\frac{3}{2}}}{l_t} \quad (6.28)$$

where l_t is the specified length scale at the inlet.

The inlet flow was defined as a constant volume flow rate and a turbulence intensity of 10% (for high flow rate) or 5% (for lower flow rate) of the mean velocity, and a turbulence length scale of 10% of the inlet hydraulic diameter was used at this location. To find out the effect of turbulence level to motion of particle, airflow with 1% and 10% turbulence intensities were also simulated. Table 6.2 shows the mass flow rate, velocities

and Reynolds numbers at the inlet (calculated using the hydraulic diameter of the nasal cavity inlet plane) for different flow rates.

Table 6.2 Velocities and Reynolds numbers for different flow rates

Flow rate (l/min)	90	60	45	30	15
mass flow rate (kg/s)	0.0018	0.0012	0.0009	0.0006	0.0003
Velocity (m/s)	18.048	12.032	9.024	6.016	3.008
Re	9821	6547	4910	3274	1637

Outlet: When using RANS, the outflow condition of a constant pressure of 0 Pa was applied at a location corresponding to the outlet opening of the nasal models.

Walls: As previously mentioned, in present simulations the wall of the nasal cavity model was assumed as hydraulically smooth, no slip wall without vasomotor changes.

Particle setting: In present simulations, many particles (10,000 of each particle diameter) with various diameters (ranging from 0.29 to and 14.14 μm) and density $\rho_p = 912 \text{ kg/m}^3$ are released in the calculated flow domain, and particle deposition positions are recorded. In order to keep the same inertial impaction parameter, $d_a^2 Q$, for comparison purposes, different particle sizes were used for particle tracking simulations involving different inhalation flow rates as described in Table 6.3. Here d_p is the particle diameter in μm and Q is the inhalation flow rate in L/min. Initial particle velocities were set equal to the fluid velocity. Since top hat profiles are used as inlet conditions, particles are randomly seeded at the circular inlet with an even spatial concentration distribution.

Particle tracking can be performed with and without turbulent dispersion. In the CFX 11.0 environment, it is controlled by setting the turbulent dispersion force as “on” or “off”. The turbulent dispersion force also can be controlled flexibly to be active in

regions where the turbulent eddy viscosity ratio is above the specified Eddy Viscosity Ratio Limit. Eddy viscosity ratio $\frac{\mu_t}{\mu}$ represents the ratio between turbulent viscosity and the dynamic viscosity of the fluid. The default value of the Eddy Viscosity Ratio Limit is 5. In the region where the eddy viscosity ratio is above the user specified limit, the flow is assumed to be turbulent, and particle tracking is performed with turbulent dispersion. Conversely, if the ratio is smaller than the limit, then the flow can be considered as laminar and no turbulent dispersion is used, thus the particle tracking is called “laminar tracking”.

There are two very important coefficients for particles in the wall boundaries setting: parallel and perpendicular restitution coefficients, which describe the actions of particles when they hit a wall. Coefficient values of 1 describe an elastic collision, while values less than 1 describe an inelastic collision. In present simulation, both coefficients were set to zero, which indicate the tracking of particles terminate when they hit the wall of nasal cavity.

Table 6.3 Physical particle diameters, d_p (μm), used in simulations for different values of the impaction parameter and flow rate

Flow rate (L/min)	Impaction parameter ($\mu m^2 L/min$)								
	6.84	27.36	109.4	246.2	437.8	684.0	985.0	1751	2736
15	0.71	1.41	2.83	4.24	5.66	7.07	8.49	11.31	14.14
30	0.50	1.00	2.00	3.00	4.00	5.00	6.00	8.00	10.00
45	0.41	0.82	1.63	2.45	3.27	4.08	4.90	6.53	8.16
60	0.35	0.71	1.41	2.12	2.83	3.54	4.24	5.66	7.07
90	0.29	0.58	1.15	1.73	2.31	2.89	3.46	4.62	5.77

6.4.2.2 *Boundary conditions and solve setting for LES*

Inlet: For the inlet condition of the present LES simulation, a top hat profile giving steady flow rates of 30, 60 and 90 L/min was used (no fluctuations were added).

Outlet: For the outlet, a zero pressure gage opening boundary condition was applied.

Initialization: The present simulation is initialized from a converged RANS velocity field as described in the previous section. No forcing is added on the computational domain. In order to eliminate the effect of initial conditions, 2 000 initial time steps were used. An additional 24,000 time steps were used in the particle deposition simulation.

Time advancement stability and accuracy were assured by adopting a time step that gave a CFL (Courant-Friedrich-Levy) number smaller than 1 throughout the computational domain, requiring a time step of typically $1.0 \mu s$. A central differencing scheme was used in the LES computations. For the time advancement, a second-order accurate implementation using a backward implicit difference formula was used. Particles were released in the frozen computational domain and deposition statistics were gathered in a single iteration using a steady mode without any model and $1 \mu s$ of physical timescale in the convergence control (see CFX 11 manual). This procedure was adopted because the dynamic particle tracking was not available in CFX 11 for the unsteady LES mode. Calculations were performed on a Pentium IV cluster having 20 nodes, requiring approximately 250 CPU hours, which shows that LES is considerably more expensive when compared with a standard RANS/EIM approach.

Chapter 7: Simulation Results

7.1 Grid convergence analysis

The importance of the assessment of the numerical uncertainty in CFD calculations has been highlighted by several authors (for example, Roache, 1998; Freitas, 2002). Uncertainty is defined as, "A potential deficiency in any phase or activity of the modeling process that is due to the lack of knowledge." (AIAA G-077-1998).

In the present report, a grid convergence analysis was performed using four different grid sizes (approximately 300 000, 1 000 000, 2 000 000, and 4 000 000 tetra and prism elements as previously stated) based on the RANS simulations results. Pressure drop through the nasal cavity, velocity distribution at certain locations of the geometry and total particle deposition through the whole nasal cavity model were chosen as verification parameters. It should be noted that grid convergence analysis in LES is not as straightforward, since one may refine the grid towards DNS resolution.

7.1.1 Pressure drop

Figure 7.1 illustrates the calculated pressure drop through the nasal cavity for 4 000 000 elements compared with the experimental data and experimental tolerance obtained by Weinhold *et al.* (2004). Although Weinhold's replica was different from the present standardized nasal geometry, simulation results are within the estimated tolerance

of the measured data for several flow rates ranging from 15 to 60 L/min, indicating a good qualitative agreement.

Figure 7.1 Simulation results of the pressure drop through nasal cavity compared with experimental results (Weinhold *et al.*, 2004)

7.1.2 Velocity profile at arbitrary location

The velocity profile over an arbitrary line at a cross section 66 mm posterior to the nostril for a constant inhalation flow rate of 30 L/min is shown separately in Figure 7.2 for different grid sizes. For higher grid sizes (2 000 000, and 4 000 000 elements), the profiles of each line look very similar indicating a good grid size adequacy; however, there still are some differences between the profiles of velocity distribution of 2 000 000, and 4 000 000 elements. This is not unexpected, and it is conjectured that the differences

in velocities are due mainly to the irregular unstructured grid meshing and the high complexity of the nasal cavity.

Figure 7.2 Grid size effect on velocity distribution on arbitrary line, which is on the cross section cross section 66 mm posterior to the nostril (flow rate = 30 L/min)

7.1.3 Grid effect on particle deposition fraction

The effect of computational grid size on calculated particle deposition fraction using turbulence tracking method for the flow rate $Q = 60$ L/min is illustrated in Figure 7.3. Specified particle diameters vary from $0.71\ \mu\text{m}$ to $7.07\ \mu\text{m}$. For smaller particles (0.71 , 1.41 , 2.12 and $2.83\ \mu\text{m}$), calculated deposition efficiencies decreased slightly when the grid size was increased, and efficiencies were very close in value for 2 000 000 and 4 000 000 elements. For larger particles (3.54 , 4.24 , 5.66 , and $7.07\ \mu\text{m}$), the calculated results for particle deposition fraction increased slightly when the grid size was increased,

and approached an asymptotic behaviour. These results suggest that coarse mesh may result in over-estimation of particle deposition for smaller particles, and a 4 000 000 element grid is sufficient for the deposition calculation.

Figure 7.3 Effect of computational grid size on particle deposition fraction ($Q = 60$ L/min)

7.1.4 Effect of iteration numbers on LES simulation results

The total deposition using LES was tested using different iteration numbers (i.e., time steps) for the inhalation flow rate of 90 L/min. Figure 7.4 shows the total particle deposition using LES as a function of the number of iterations for two different particle sizes ($d_p = 3.46$ and $d_p = 1.73 \mu\text{m}$). It can be seen that the total deposition fraction (DF) decreases when the iteration number is increased, and the relationship between these two

variables shows an asymptotic trend. After 1.5×10^4 time iterations, total particle deposition fraction oscillates about an average value ($DF=0.44$ for $d_p = 3.46$ and ($DF=0.12$ for $d_p = 1.73$).

Figure 7.4 LES results of total particle deposition fraction as function of number of iterations

7.2 Sensitivity analysis

As mentioned in section 4.3.2, when using the RANS/EIM approach, the turbulence intensity and length scale are both specified for inlet boundary condition. There are several other fluid values that can be set, apart from turbulence intensity and length scale, for the calculation domain when using CFX software, such as: intensity and eddy viscosity ratio, k and epsilon, or intensity and auto compute length. Based on

fundamental of fluid dynamics, when the turbulence intensity and length scale are both specified for inlet boundary condition, the inlet turbulent kinetic energy, k , dissipation of turbulence kinetic energy, ε , eddy viscosity ratio, $\frac{\mu_T}{\mu}$, are also set.

The effect of fractional turbulence intensity I at the inlet on particle deposition fraction, with flow rate $Q = 60$ L/min and inlet length scale kept constant (10% of the hydraulic diameter of inlet), was investigated. The parameters for this investigation were given in Table 7.1.

Table 7.1 Calculation parameters for sensitivity analysis (constant inlet length scale)

Flow rate (L/min)	Velocity (m/s)	length scale (m)	length scale ratio	turbulence intensity I	k (m^2/s^2)	$\frac{\mu_T}{\mu}$ (m^2/s^3)	viscosity ratio
60	12.03	0.0008	0.1	0.01	0.021	2.612954	0.888
60	12.03	0.0008	0.1	0.05	0.543	326.6193	4.4388
60	12.03	0.0008	0.1	0.1	2.172	2612.954	8.8768
60	12.03	0.0008	0.1	0.15	4.886	8818.72	13.3148

It can be seen from the Figure 7.5 that when length scale at the inlet is kept constant, the increase in fractional turbulence intensity at the inlet enhanced the particle deposition fraction within a reasonable range, which illustrates the influence of turbulence on particle deposition fraction in the human nasal cavity.

Figure 7.5 Effect of fractional turbulence intensity I on particle deposition fraction ($Q = 60$ L/min, length scale at inlet = $D_h/10$)

Similarly, the effect of inlet length scale ratio on particle deposition fraction, with flow rate $Q = 60$ L/min and constant fractional turbulence intensity ($I = 0.1$), was investigated using the parameters shown in Table 7.2.

Table 7.2 Calculation parameters for sensitivity analysis (constant inlet length scale)

Flow rate (L/min)	Velocity (m/s)	turbulence intensity I	length scale (m)	length scale ratio	k (m^2/s^2)	ε (m^2/s^3)	viscosity ratio
60	12.03	0.1	0.0004	0.05	2.172	5225.908	4.438
60	12.03	0.1	0.0008	0.1	2.172	2612.954	8.876
60	12.03	0.1	0.0016	0.2	2.172	1306.477	17.753
60	12.03	0.1	0.004	0.5	2.172	522.591	44.381

The results of this testing are shown in Figure 7.6. It can be seen that when the length scale ratio changes from 0.05 to 0.2, the results of nasal particle deposition were

almost constant, indicating that the chosen length for the inlet boundary (10% of hydraulic diameter) is reasonable.

Figure 7.6 Effect of inlet length scale ratio on particle deposition fraction ($Q = 60$ L/min, fractional turbulence intensity $I = 0.1$)

7.3 Airflow structure

7.3.1 Velocity and kinetic energy

7.3.1.1 Distribution of velocity and turbulence kinetic energy

Typical air flow characteristics, shown here for the inhalation flow rate of 60 L/min, can be seen from the distribution of velocity (Figure 7.7a) and turbulence kinetic energy (Figure 7.7b), at the inlet and outlet, and along 10 coronal planes of the novel standardized nasal airway model.

Figure 7.7 Velocity distribution (a) and turbulence kinetic energy distribution (b) in standardized human nasal cavity along coronal planes (flow rate, $Q = 60$ L/min, 4 000 000 elements)

Air enters the nasal cavity from the nostril and its mean velocity changes as it flows through the nasal cavity due to the change in cross-sectional area. The air impinges and circumvents the nasal valve region and the three turbinates, which have the most complex geometry of any structure in the nasal cavity (see Figure 1.1 for reference), and generates some turbulence kinetic energy and leaves the nasal cavity through the outlet. Observing the velocity distribution in one cross-sectional plane (Figure 7.7a), velocities at the

superior airway, middle meatus, and inferior airway are much higher than in other regions, which can be attributed to the smaller flow cross-sectional areas and downstream flow patterns in these regions. After passing through the nasal valve, the air is accelerated and a small amount of turbulence kinetic energy is generated (see Figure 7.7b plane 4 for reference). However, this turbulent energy quickly dissipates, and after plane 6 it drops to near zero, which indicates that the downstream flow appears to be essentially laminar.

7.3.1.2 Streamwise distribution of mean velocity magnitude

The streamwise distribution of mean velocity, averaged over the local cross-sectional area, in the standardized human nasal cavity is shown in Figure 7.8 for inhalation flow rates of 30, 45 and 60 L/min. The same inlet boundary conditions (i.e., 5% of the mean velocity and a turbulence length scale of 10% of the inlet hydraulic diameter) were used to study the streamwise distribution of mean velocity for three different flow rates as were used in the sensitivity analysis.

It can be seen that the mean velocities of the cross-section planes for three different inhalation flow rates share similar trends due to change in cross-sectional area (the reference for the cross-sectional area of the novel standardized nasal airway geometry is shown in Figure 3.13). The bigger the cross-sectional area of the cross-section plane, the smaller the magnitude of the mean velocity becomes. The peak value of the mean velocity appears at a dimensionless distance from the nostril equal to 0.25, coinciding with the location of smallest cross-sectional area, which is coinciding with the location of the nasal valve.

Figure 7.8 Streamwise distribution of mean velocity magnitude

7.3.1.3 Streamwise distribution of turbulence kinetic energy

The streamwise distribution of turbulence kinetic energy, k , averaged over the local cross-sectional area is shown in Figure 7.9 for inhalation flow rates of 45 L/min and 60 L/min. The inlet boundary conditions for the turbulence kinetic energy measurements were 1%, 5% and 10% of the mean inlet velocity. For each flow rate, results for different turbulence intensities were sensitive to the inlet conditions, meaning higher values of turbulence kinetic energy intensity at the inlet resulted in higher values throughout the domain. Despite the different levels of turbulence at the inlet, the profiles of mean turbulence kinetic energy along the standardized human nasal cavity for each flow rate share similar trends, and they reach a small peak value at a dimensionless

distance from the nostril equal to 0.35 (coinciding with the beginning and the frontal location of the turbinates).

Figure 7.9 Average cross-stream turbulence kinetic energy for low (1%), middle (5%) and high (10%) turbulence intensities at inlet

Table 7.3 summarizes the peak values of turbulence kinetic energy for each flow rate for high (10%), middle (5%) and lower (1%) turbulence intensities. The data in Table 7.3 indicate that the turbulence models are necessary in the simulation at these inhalation

flow rates. Beyond a dimensionless distance from the nostril of about 0.6, the turbulence kinetic energy drops to near zero and the flow in the domain can be considered to be laminar in nature. It also can be seen that near the outlet boundary, some turbulence kinetic energy is generated, caused by the impaction of air on the wall after it leaves the three turbinates.

Table 7.3 The values of turbulence kinetic energy at the small peak for low, middle and high turbulence intensities at the inlet

Flow rate (L/min)	Turbulence kinetic energy for low turbulence intensity, 1% (m²kg/s²)	Turbulence kinetic energy for middle turbulence intensity, 5% (m²kg/s²)	Turbulence kinetic energy for high turbulence intensity, 10% (m²kg/s²)
90	1.068	2.136	2.295
60	0.395	0.592	0.707
45	0.124	0.186	0.252
30	0.016	0.024	0.032

7.3.2 Particle motion and deposition patterns

Figure 7.10 shows the complex trajectories and travel distances of particles for the flow rate of 60 L/min. For illustrative purposes and clarity, only 600 of the 10 000 calculated trajectories of particles are shown in each of Figure 7.10.a-c for the RANS/EIM “turbulent tracking”, “mean flow tracking” and LES simulation, respectively.

It can be seen that there is a recirculation zone at the anterior region of the nasal cavity near the nostril. On close inspection, it can be seen from the “turbulent tracking” results that fewer particles reach the outlet (meaning more deposition) when compared to the “mean flow tracking” approach. The particle trajectories using LES particle tracking are similar to the turbulent tracking data, while the velocity fluctuations can be observed from LES particle trajectories.

Figure 7.10 Particle tracking with particle travel distance ($Q = 60$ L/min, $d_p = 7.071$ μm , $d_p^2 Q = 2736$). (a) RANS/EIM turbulence tracking. (b) RANS/EIM mean flow tracking. (c) LES.

7.3.3 Simulated results of total particle deposition fraction

7.3.3.1 Effect of different RANS model on particle deposition fraction

Particle deposition fraction results using the SST model, standard $k-\omega$ model and standard $k-\varepsilon$ model with turbulent particle tracking are shown in Figure 7.11. Results of the SST model and the $k-\omega$ model show the same trends with a slight over-prediction for small inertial impaction parameter values and under-prediction for large inertial impaction parameter values. The results of the $k-\varepsilon$ model show significant over-

prediction for the whole range of inertial impaction parameters and cannot reveal the important role of inertial impaction in the deposition of particles. This suggests that the standard $k-\varepsilon$ model is not appropriate for an airflow and particle deposition simulation of the geometrically complex nasal cavity. The results of the RANS/EIM approach in the present work were all obtained using the $k-\omega$ SST model. They are discussed in detail in section 7.3.3.2 with present measurement results.

Figure 7.11 Particle deposition fraction results using different RANS model (turbulent tracking method)

7.3.3.2 Simulated results of total particle deposition fraction

Simulated deposition results using the mean flow tracking method (i.e. without turbulent

diffusion), the turbulent tracking method (i.e. with turbulent diffusion), and LES for different flow rates (30, 60 and 90 L/min using the same grid resolution of 4 000 000 tetrahedric elements) are shown in Figure 7.12, together with data from the current experiments. For the RANS based simulations, the air flow was calculated using the SST turbulence model with turbulence intensity of 5% of the mean velocity at inlet location.

The numerical results shows good agreement when compared with the present *in vitro* measurements, especially for inertial impaction parameter ranged 100~800. Close inspection of the graph reveals that the deposition results using RANS simulations with either turbulent tracking (using the eddy interaction model) or mean flow tracking are quite similar, indicating that inertial impaction is the dominant mode of deposition in the nasal cavity, even for these relatively small particles.

For larger impaction parameters ($d_a^2 Q > 1000$), the numerical simulations show a slight under-prediction of the present *in vitro* deposition data. This is likely attributable to an effect of wall roughness. In the numerical simulation, the boundary condition for the wall of the nasal cavity was specified as smooth, whereas there is a small but unavoidable wall roughness along the inner wall of the *in vitro* model due to manufacturing. Some of this difference might also be attributable to differences between actual inlet conditions in the experiment and those chosen for the simulations, although this effect is thought to be less significant as discussed in Figure 5.2 of section 5.1.1.2.

For smaller values of the inertial parameter ($d_a^2 Q < 200$), the RANS turbulent tracking simulations corresponding to an inhalation flow rate of 90 L/min deviated from the rest of the data. Similar errors have been observed in other simulations that have appeared in some published works (e.g., Tang et al., 2004, Liu et al., 2007), and are

thought to be related to the linear interpolation used to determine the fluid velocity and other turbulence statistics at the particle's location. The inaccuracies in the linear interpolation arise during the integration of the particle equation of motion. Inaccuracies might arise on account of the mesh elements attached to the walls, which affect deposition of particles with a small inertial parameter.

Figure 7.12 Deposition results using different simulation methods compared with measured data

In addition to different particle diameters, particles of different densities are used to analyse the influence of particle density on the deposition fraction. The deposition

curves, created using the same tracking method, completely overlap when they are plotted as a function of the impaction parameter, no matter what the density is.

The comparison of simulation results with previous deposition simulations of several other researchers (Inthavong et al., 2006; Tian et al., 2007; Shi et al., 2007; Shanley et al., 2008) is shown in Figure 7.13. Although the nasal cavity models of cited works were generated from different subjects (Inthavong et al., 2006 and Tian et al., 2007: CT scans of a 25-year-old healthy, non-smoking Asian male; Shi et al., 2007: MRI scans of a 53-year-old non-smoking Caucasian male originating from Swift (1991); Shanley et al., 2008: MRI scans of an anonymous, healthy, adult male human subject), these results show consistent trends. It can be noted that the current simulation results fall in the middle range of other published numerical predictions of particle deposition. Given that the current numerical results match the present experimental data using the same standardized nasal model as shown in Figure 7.12, this provides additional support for the discussion of differences among in vitro deposition data from different geometries presented in Section 2.3.2.2 and Section 5.1.1.2 above. Specifically, the simulations of Shi et al. (2007), using the geometry of Swift (1991) also used by the range of studies corresponding to blue symbols in Figure 7 above, span the current simulated data as the effects of wall roughness are modeled numerically. At high values of the impaction parameter, the simulations of Shanley et al. (2008) and Tian et al. (2007) also fall on either side of the current data. Although these studies considered different nasal geometries, both modeled deposition using the Lagrangian particle tracking algorithm within the commercial FLUENT CFD software for similar flow ranges and assuming laminar flow. The sigmoid trends of deposition fraction are quite similar between these

studies and the differences in magnitude of deposition fraction at fixed values of the impaction parameter are a strong indication of the importance of inter-subject variability, which in this case spans the data for the standardized geometry.

Figure 7.13 Comparison of current simulation results with published simulation data from other researchers

7.3.4 Regional particle deposition fraction results

7.3.4.1 Simulated results of regional particle deposition fraction distribution

A quantitative analysis of regional distribution of particle deposition within the nasal cavity was also performed in the present work. Figure 7.14.a-c illustrates the LES simulation results of regional particle deposition fraction on the surface of the nasal

passage for inhalation flow rates of 30, 60, and 90 L/min with a variety of different particle sizes. For this range of flow rates, the largest particles (with diameters ranging from 5.77 - 10.0 μm) deposit most significantly in the first 30% of the length of the nasal cavity. Moreover, in the anterior region, the majority of deposited particles impact on the cavity walls near the location of the nasal valve (i.e., at a dimensionless distance from the nostril equal to approximately 0.3). These results highlight the critical importance of considering the geometry in the region of the nostrils and nasal valve in determining deposition rates.

In the context of drug delivery, these results suggest that while it may be relatively easy to target deposition in the early part of the nasal cavity, it is much more difficult to deposit particles in the middle and posterior cavity without having them carry on through the nasopharynx. It is also noted by Shanley et al. (2008) through simulations that smaller particles mostly escape into the nasopharynx, while larger particles deposit preferentially in the anterior region with increasing Stokes number. Considering the fact that the turbinates and olfactory region of the nasal cavity are the locations where most of drug absorption occurs (Illum, 2000), the desirable particles sizes for drug delivery for different flow rates could be obtained by the regional distribution of the deposited particles shown in Figure 7.14. For example, at the lowest flow rate of 30 L/min (Figure 7.14a), deposition of 10 μm particles shows a bimodal distribution with a secondary peak at approximately 60% of the distance into the cavity. For smaller sized particles, there is an abrupt drop in deposition for all three flow rates. The limited deposition that occurs is also more evenly distributed throughout the nasal cavity.

Figure 7.14 Regional particle deposition fraction for different sized particles calculated from LES simulations for inhalation flow rates of: (a) 30 L/min, (b) 60 L/min, and (c) 90 L/min

7.3.4.2 Comparison of measured and computed regional particle deposition fraction

Figure 7.15 shows a comparison of measured particle deposition and computed deposition from LES simulations within each region for a range of particle diameters and flow rates. The experiments and simulations agree quite well, although the LES results show a slight under-prediction for larger particles in the anterior region that is most pronounced at higher flow rates. As discussed above, this is most likely attributed to differences in actual and simulated wall roughness as well as any potential influence of subgrid scale turbulence on particle dispersion and deposition.

Figure 7.15 Measured and LES results for regional deposition for various sizes of particles at inhalation flow rates of: (a) 30 L/min, (b) 60 L/min, and (c) 90 L/min

7.3.4.3 Fitting curves for regional particle deposition fraction

For any given particle diameter and flow rate, more deposition occurs in the anterior region than in either the middle or posterior regions; however, the ratio of deposition among regions varies with particle diameter. These results can be correlated with the impaction parameter as shown in Figure 7.16.

The curves on Figure 7.16 are empirical, second order polynomial fits ($DF = a + b \cdot IP + c \cdot IP^2$), and the values of the constants a , b , and c are included in Table 7.4. Deposition in the posterior region is essentially negligible because the posterior part contains less than 10% of the total length of the nasal cavity.

Figure 7.16 Particle deposition in the three regions of the nasal cavity correlated with the impaction parameter, $d_a^2 Q$

The trends of deposition as a function of the impaction parameter reveal how the relative amounts of particles deposited in each region can vary under different conditions.

Peak deposition in the middle region occurs at an impaction parameter of approximately $1500 \mu\text{m}^2\text{L}/\text{min}$; however, only 10% of the total particles are deposited at this condition, which equates to $\sim 17.5\%$ of the total deposited particles. At an impaction parameter of $200 \mu\text{m}^2\text{L}/\text{min}$, even fewer (only $\sim 3.7\%$) of the total particles entering the nasal cavity are deposited in the middle region, but this amount represents a much larger fraction ($\sim 42\%$) of the total particles that are deposited. In any case, regional deposition results suggest that significant quantities of particles can be deposited in the anterior part of the nasal cavity, thus it is important to consider the geometry of the nasal inlet and the nasal valve when modeling the nasal cavity.

Table 7.4 Curve fit parameters for regional deposition data

Curve	a	b ($\text{min}/\mu\text{m}^2\text{L}$)	c ($\text{min}^2/\mu\text{m}^4\text{L}^2$)	r^2
Anterior region, experimental data	-0.035	4.404×10^{-4}	-5.179×10^{-8}	0.982
Anterior region, LES data	-0.024	3.594×10^{-4}	-4.411×10^{-8}	0.991
Middle region, experimental data	0.016	1.112×10^{-4}	-3.375×10^{-8}	0.718
Middle region, LES data	0.013	1.048×10^{-4}	-3.010×10^{-8}	0.901

7.3.5 Effect of size of nasal cavity on particle deposition fraction

Simulation on total particle deposition fraction was also performed using RANS/EIM approach on two nasal cavities that were shrunk for purposes of comparison. The standardized nasal cavity model was scaled using factors of 0.8 and 0.4, which provided 20%-shrunk and 80%-shrunk nasal cavity models, respectively. The simulation settings for the shrunk nasal cavity model are the same as those described in Chapter 6. Figure 7.17 shows the simulation results on the two shrunk nasal cavity models, and the results

using standardized nasal model and *in vivo* data summarized by Cheng (2003) are also presented. It can be seen that the deposition fraction for the shrunk models are higher than the values of the standardized model for the same impaction parameter. The results of 20%-shrunk model are close to the lower confidence level interval line, and results of 40%-shrunk model are close to the averaged *in vivo* data (Cheng, 2003). It is conjectured here that the difference in deposition is due to nasal airway geometry. Smaller nasal cavity geometry (smaller minimum cross-sectional area) results in higher particle deposition, which is consistent with the conclusion drawn by Swift (1981), in which deposition fraction for the infant casts was higher than in the adult casts for the same impaction parameter.

Figure 7.17 Deposition results using shrunk nasal cavity models

Chapter 8: Conclusions and Future work

8.1 Conclusions

A novel, standardized nasal cavity model has been created by carefully aligning and processing 30 sets of CT scans of human nasal cavities. Through digital image processing, the left and right nasal cavities were separately analyzed to produce a standardized nasal cavity model that closely matched the median cross-sectional area characteristic of the 60 individual geometries, while retaining the unique geometric features of the human nasal cavity. Using this “Carleton-Civic” standardized geometry of the human nasal cavity, airflow patterns were simulated, and aerosol deposition was studied both numerically and experimentally.

Deposition data from *in vitro* experiments in the Carleton-Civic standardized human nasal cavity geometry fell within available published *in vitro* data from individual subjects. Data also correlated well with cited *in vivo* data, although deposition was lower for identical values of the impaction parameter. This difference is attributable to a combination of the absence of nasal hairs in the *in vitro* model, differences in wall roughness, and unquantified uncertainties in the cited *in vivo* measurements.

Simulated results of airflow show that independent of the turbulence level at the inlet, non-negligible turbulence kinetic energy will be present in the first half of the computational domain, indicating that turbulence models are necessary for the range of the inhalation flow rates (15–90 L/min) simulated in this study. For each flow rate, the profile of mean turbulence kinetic energy shows similar trends, and the peak value of

mean turbulence kinetic energy appears at a dimensionless distance from the nostril equal to 0.35, which coincides with the beginning and the frontal location of the turbinates. Further into the cavity, the turbulent energy quickly dissipates, indicating that the downstream flow is essentially laminar.

Results of deposition experiments were generally well-predicted by the numerical simulations, with some exceptions for large values of the impaction parameter. Regional deposition data derived from the standardized model revealed that, for the range of conditions studied, the majority of deposition occurs in the anterior region of the nasal cavity and specifically in the region of the nasal valve, and that the relative amounts of deposition within the nasal cavity vary significantly with impaction parameter. Both measurements and LES results of regional deposition efficiencies suggest that the geometry of the nasal inlet through to the nasal valve is critical in correctly modeling deposition in the nasal passageway. Considering the important role of the turbinates in the absorption of drug delivered to the nasal cavity, the trends of the regional particle fractions have significance for the determination of preferred particle sizes and could have application in pharmaceutical research.

The Carleton-Civic nasal geometry produced in this work will be useful to researchers and physicians in studying deposition of inhaled aerosols, and also will serve as a candidate standard for aerosol deposition testing in the pharmaceutical industry. The use of a standardized geometry could aid in development of more accurate experimental and numerical predictions of pharmaceutical aerosol deposition and raises possibilities for new insight, faster development, and reduced costs of better drug delivery devices. As a diagnostic tool, the CT scan of a patient could be processed and compared against

this standardized model to indicate deviation from the present average characteristic values, such as cross-sectional area, nostril area, or generic shape. The specific procedure developed in this study could also be applied in the future in comprehensive studies involving different identifiable groups in the population, as more CT scan or MRI data become available.

8.2 Future work

Despite the success of this project, several important research questions remain in the quest to fully understand and predict aerosol deposition in the human nasal cavity. Some of these future research areas are as follows:

1. Airflow patterns have been investigated numerically using the novel standardized human nasal cavity model. Fluid flow measurements using PIV (Particle Image Velocimetry) would be helpful to validate present simulation results of airflow patterns.
2. In present work, the inertial parameter was changed by mostly changing the flow rate instead of having larger particles. Further investigation on particle deposition for lower inhalation flow rates and larger particles would be worth performing.
3. Present measured particle deposition fractions were obtained using a physical replica, which was divided into three parts. While this is an improvement over most previous studies which have only measured total deposition, the present investigation of regional deposition results was still limited.

Based on results of this work, a physical nasal model could be manufactured and assembled to obtain more details of the regional particle deposition fraction in regions of specific interest, i.e., within the existing anterior section.

4. In the present simulations, the inner wall of the nasal cavity model was simplified as a hydraulically smooth wall without nasal hairs. From the discussion in Chapter 5 and Chapter 7, it can be seen that the effect of nasal hairs and wall roughness on airflow patterns and particle depositions patterns are non-negligible. Improved simulation methodology could take these factors into account and to provide more realistic results of particle deposition and airflow patterns. Also, experimentally investigating the influence of nasal hairs and wall roughness would be very helpful to validate simulation results.

5. In present simulation and experimental work, nasopharynx was not included in the standardized nasal cavity model. An improved nasal model could be generated including the nasopharynx and could be used to study its influence on the airflow patterns and deposition patterns in the nasal cavity.

6. As discussed in section 2.3.2.2, Häußermann et al. (2002) pointed out that human cyclic breathing patterns had significant influences on the particle deposition for flow rates higher than 10 L/min. The influence of realistic human breathing patterns on particle deposition could be investigated in the future using the standardized human nasal cavity model.

7. Building on the methodology used to create the Civic-Carleton standardized human nasal cavity, an intensive study could be performed to investigate the influence of inter-subject variability of nasal anatomic geometry

on particle deposition. Ideally, the relationship between nasal anatomic characteristic dimensions for subgroups of population (such as gender, age, ect.) and particle deposition patterns could be found and that could be applied for the prediction of particle deposition in human nasal cavity.

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Appendix A: Shear Stress Transport (SST) Turbulence Model

The standard version of the $k-\omega$ model can be described as follows:

Continuity Equation,

$$\frac{\partial U_i}{\partial x_i} = 0. \quad (\text{A.1})$$

Momentum Equation,

$$\frac{\partial U_i}{\partial t} + U_j \frac{\partial U_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j} \left[(\nu + \nu_T) \left(\frac{\partial U_i}{\partial x_j} + \frac{\partial U_j}{\partial x_i} \right) \right] \quad (\text{A.2})$$

Turbulence Kinetic Energy,

$$\frac{\partial k}{\partial t} + U_j \frac{\partial k}{\partial x_j} = P_k - \beta_1 k \omega + \frac{\partial}{\partial x_j} \left[(\nu + \sigma_1 \nu_T) \frac{\partial k}{\partial x_j} \right] \quad (\text{A.3})$$

Specific Dissipation Rate,

$$\frac{\partial \omega}{\partial t} + U_j \frac{\partial \omega}{\partial x_j} = \alpha_1 \frac{\omega}{k} P_k - \beta'_1 \omega^2 + \frac{\partial}{\partial x_j} \left[(\nu + \sigma'_1 \nu_T) \frac{\partial \omega}{\partial x_j} \right] \quad (\text{A.4})$$

The $k-\omega$ model assumes that the turbulence viscosity is linked to the turbulence kinetic energy and turbulent frequency via the relation:

$$\mu_T = \rho \frac{k}{\omega}. \quad (\text{A.5})$$

To get the SST model, the $k-\varepsilon$ model is developed as:

$$\frac{\partial k}{\partial t} + U_j \frac{\partial k}{\partial x_j} = P_k - \beta_2 k \omega + \frac{\partial}{\partial x_j} \left[(\nu + \sigma_2 \nu_T) \frac{\partial k}{\partial x_j} \right] \quad (\text{A.6})$$

$$\frac{\partial \omega}{\partial t} + U_j \frac{\partial \omega}{\partial x_j} = \alpha_2 \frac{\omega}{k} P_k - \beta'_2 \omega^2 + \frac{\partial}{\partial x_j} \left[(\nu + \sigma'_2 \nu_T) \frac{\partial \omega}{\partial x_j} \right] + 2 \frac{\sigma'_2}{\omega} \frac{\partial k}{\partial x_j} \frac{\partial \omega}{\partial x_j} \quad (\text{A.7})$$

with model constants:

$$\beta_1 = 0.09, \quad \alpha_1 = 5/9, \quad \beta'_1 = 3/40, \quad \sigma_1 = 0.5, \quad \sigma'_1 = 0.5$$

$$\beta_2 = 0.09, \quad \alpha_2 = 0.44, \quad \beta'_2 = 0.0828, \quad \sigma_2 = 1, \quad \sigma'_2 = 0.856$$

The production rate of turbulence is given by:

$$P_k = \nu_T 2S_{ij} \frac{\partial U_i}{\partial x_j} \quad (\text{A.8})$$

The mean-strain-rate tensor is defined by:

$$S_{ij} = \frac{1}{2} \left(\frac{\partial U_i}{\partial x_j} + \frac{\partial U_j}{\partial x_i} \right) \quad (\text{A.9})$$

The SST turbulence model is obtained by:

$$\Phi_3 = F_1 \Phi_1 + (1 - F_1) \Phi_2 \quad (\text{A.10})$$

in which, Φ_1 is the standard $k-\omega$ model, Φ_2 is the developed $k-\varepsilon$ model. The blending functions F_l is equal to one near the surface and switches over to zero inside the boundary layer (i.e., a function of the wall distance) and ensure a smooth transition between the two models and are critical to the success of the method. Their formulation is based on the distance to the nearest surface and on the flow variables.

$$F_1 = \tanh(\arg_1^4) \quad (\text{A.11})$$

with

$$\arg_1 = \min \left(\max \left(\frac{\sqrt{k}}{\beta' \omega y}, \frac{500\nu}{y^2 \omega} \right), \frac{4\rho k}{CD_{KW} \sigma_{\omega 2} y^2} \right) \quad (\text{A.12})$$

where y is the distance to the nearest wall and ν is the kinematic viscosity and:

$$CD_{K\omega} = \max \left(2\rho \frac{1}{\sigma_{\omega 2} \omega} \frac{\partial k}{\partial x_i} \frac{\partial \omega}{\partial x_i}, 1.0 \times 10^{-10} \right) \quad (\text{A.13})$$

Additionally, Kinematic Eddy Viscosity is defined in order to get correct transport characteristic:

$$\nu_T = \frac{\alpha_1 k}{\max(\alpha_1 \omega, SF_2)} \quad (\text{A.14})$$

in which,

$$F_2 = \tanh(\arg_2^2) \quad (\text{A.15})$$

with

$$\arg_2 = \max \left(\frac{2\sqrt{k}}{\beta' \omega y}, \frac{500\nu}{y^2 \omega} \right) \quad (\text{A.16})$$

F_2 is a blending function similar to F_1 , which restricts the limiter to the wall boundary layer, as the underlying assumptions are not correct for free shear flows.

Appendix B: Large Eddy Simulation

For an incompressible flow of a Newtonian fluid, the filtered Navier-Stokes Equations solved by the LES are given by the continuity equation

$$\frac{\partial \bar{u}_i}{\partial x_i} = 0 \quad (\text{B.1})$$

and the momentum equation

$$\frac{\partial \bar{u}_i}{\partial t} + \frac{\partial}{\partial x_j} (\bar{u}_i \bar{u}_j) = -\frac{1}{\rho} \frac{\partial \bar{p}}{\partial x_i} - \frac{\partial \tau_{ij}}{\partial x_j} + \nu \frac{\partial^2 \bar{u}_i}{\partial x_i \partial x_j}. \quad (\text{B.2})$$

where $\bar{u}_i$ are the three Cartesian velocity components of the resolved large scales, $\bar{p}$ is the corresponding pressure and Re is the Reynold number. During the filtering process, an additional term appears in the momentum equation, *i.e.*, the subgrid scale (SGS) stress term, τ_{ij} , which should be modeled and describes the influence of the non-resolved small-scale structures on the large eddies. The SGS stress term is given by

$$\tau_{ij} = \overline{u_i u_j} - \bar{u}_i \bar{u}_j \quad (\text{B.3})$$

The SGS used here was proposed by Smagorinsky (1963) and Lilly (1966). The SGS stresses are related to the strain rate tensor by a SGS viscosity, ν_T :

$$\tau_{ij} - \frac{1}{3} \delta_{ij} \tau_{kk} = 2\nu_T \bar{S}_{ij} \quad (\text{B.4})$$

where δ_{ij} is the Kronecker delta. The SGS viscosity is given by:

$$\nu_T = \rho (C_s D_{wall} \Delta)^2 |\bar{S}| \quad (\text{B.5})$$

where C_s is the Smagorinsky constant ($C_s = 0.1$ in the present simulation), D_{wall} the Van Driest wall damping factor, Δ the filter width and $|\bar{S}|$ the magnitude of the large-scale strain-rate tensor

$$\bar{S}_{ij} = \frac{1}{2} \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right) \quad (\text{B.6})$$

This combination (Smagorinsky / Van Driest wall damping) proved to be effective in the simulation of particle deposition on the internal walls of a vertical pipe flow. More complex SGS models have appeared in the literature (for example, the dynamic SGS eddy viscosity models), but they are beyond the scope of the present work.

Glossary

Asbestosis

A chronic inflammatory and fibrotic medical condition affecting the parenchymal tissue of the lungs caused by the inhalation and retention of asbestos fibers.

Choana

The posterior nasal aperture, the opening into the nasopharynx.

Coronal

Of, relating to, or having the direction of the coronal suture or of the plane dividing the body into front and back portions.

Gastrointestinal

Of or relating to the stomach and intestines.

Hygroscopicity

The ability to attract water molecules from the surrounding environment through either absorption or adsorption.

Krypton

A chemical element with the symbol Kr and atomic number 36.

Lysozyme

An enzyme occurring naturally in egg white, human tears, saliva, and other body fluids, capable of destroying the cell walls of certain bacteria and thereby acting as a mild antiseptic.

Monodisperse

A collection of objects are called monodisperse if they have the same molecular mass.

Nasopharynx

The uppermost part of the pharynx, that lies behind the nose and above the level of the soft palate: it differs from the oral and laryngeal parts of the pharynx in that its cavity always remains patent (open).

Olfactory

Of or relating to the sense of smell.

Olfactory region

The area on and above the superior turbinates and on the adjoining nasal septum where the mucous membrane has olfactory epithelium and olfactory glands.

Olfactory bulb

One of two enlargements at the terminus of the olfactory nerve at the base of the brain just above the nasal cavities.

Otolaryngology

The branch of medicine that deals with diagnosis and treatment of diseases of the ear, nose, and throat.

Post-mortem

Of or relating to a medical examination of a dead body.

Rhinometry

A technique for measuring the nose or its cavities.

Silicosis

A form of occupational lung disease caused by inhalation of crystalline silica dust, and is marked by inflammation and scarring in forms of nodular lesions in the upper lobes of the lungs.

Sinus

Various air-filled cavities in the bones of the skull, especially one communicating with the nostrils.

Stereolithography

A three-dimensional printing process that makes a solid object from a computer image by using a computer-controlled laser to draw the shape of the object onto the surface of liquid plastic.

Stochastic

Random. Non-deterministic behaviour.

Therapeutic

Tending to cure or restore to health.

Threshold

The point that must be exceeded to begin producing a given effect or result or to elicit a response.

Turbinate

The scroll-shaped turbinate bones in the nasal passages (also referred to as conchae).